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## Genetic influences on schizophrenia and subcortical brain volumes: large-scale proof-of-concept and roadmap for future studies

Barbara Franke<sup>#2,3,4</sup>, Jason L Stein<sup>#5,6</sup>, Stephan Ripke<sup>#7,8,9</sup>, Verner Anttila<sup>7,8</sup>, Derrek P Hibar<sup>5</sup>, Kimm J E van Hulzen<sup>2,4</sup>, Alejandro Arias-Vasquez<sup>2,3,4,10</sup>, Jordan W Smoller<sup>8,11,12</sup>, Thomas E Nichols<sup>13,14</sup>, Michael C Neale<sup>15</sup>, Andrew M McIntosh<sup>16</sup>, Phil Lee<sup>8,11,12</sup>, Francis J McMahon<sup>17</sup>, Andreas Meyer-Lindenberg<sup>18</sup>, Manuel Mattheisen<sup>19,20,21</sup>, Ole A Andreassen<sup>22,23</sup>, Oliver Gruber<sup>24</sup>, Perminder S Sachdev<sup>25,26</sup>, Roberto Roiz-Santiañez<sup>27,28</sup>, Andrew J Saykin<sup>29,30,31</sup>, Stefan Ehrlich<sup>32</sup>, Karen A Mather<sup>25</sup>, Jessica A Turner<sup>33,34</sup>, Emanuel Schwarz<sup>18</sup>, Anbupalam Thalamuthu<sup>25</sup>, Yin Yao Shugart<sup>17</sup>, Yvonne YW Ho<sup>35</sup>, Nicholas G Martin<sup>35</sup>, Margaret J Wright<sup>35,36</sup>, Schizophrenia Working Group of the Psychiatric Genomics Consortium<sup>37</sup>, ENIGMA Consortium<sup>37</sup>, Michael C O'Donovan<sup>#39,40</sup>, Paul M Thompson<sup>#5</sup>, Benjamin M Neale<sup>#7,8,11,41</sup>, Sarah E Medland<sup>#35</sup>, and Patrick F Sullivan<sup>#42,43,44</sup>

<sup>2</sup> Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands <sup>3</sup> Department of Psychiatry, Radboud University Medical Center, Nijmegen, The Netherlands <sup>4</sup> Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands <sup>5</sup> Imaging Genetics Center, Mark and Mary Stevens Neuroimaging & Informatics Institute, Keck School of Medicine of the University of Southern California, Marina del Rey, CA, USA <sup>6</sup> Neurogenetics Program, Department of Neurology, UCLA School of Medicine, Los Angeles, USA <sup>7</sup> Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA <sup>8</sup> Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA <sup>9</sup> Department of Psychiatry and Psychotherapy, Charité Universitätsmedizin Berlin, CCM, Berlin, Germany <sup>10</sup> Department of Cognitive Neuroscience, Radboud University Medical Center, Nijmegen, The Netherlands <sup>11</sup> Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, MA, USA <sup>12</sup>

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*Correspond with:* Barbara Franke, PhD, Department of Human Genetics (855), Radboud University Medical Center, Nijmegen, The Netherlands. V: +31-24-3610181, ; Email: [barbara.franke@radboudumc.nl](mailto:barbara.franke@radboudumc.nl) Patrick F Sullivan, MD FRANZCP, Departments of Genetics, CB #7264, 5097 Genomic Medicine Building, University of North Carolina, Chapel Hill, NC 27599-7264 USA. ; Email: [pf@sullivan@med.unc.edu](mailto:pf@sullivan@med.unc.edu). V: +1 919-966-3358.

<sup>37</sup>See Consortium collaborator lists

### URLs

Psychiatric Genomics Consortium (<http://pgc.unc.edu>); ENIGMA (<http://enigma.ini.usc.edu>); 1000 Genomes Project imputation panel (<http://mathgen.stats.ox.ac.uk/impute>); matSpD interface (<http://genepi.qimr.edu.au/general/daledN/matSpD>).

### Conflicts of Interest

Several of the authors/contributors are employees of companies: Johnson and Johnson, Pfizer (C.R.S., J.R.W., H.S.X.), F. Hoffman-La Roche (E.D., L.E.), Eli Lilly (D.C., Y.M., L.N.), Janssen (S.G., D.W., Q.S.L.), and deCODE genetics (S.G., K.S., H.S.). P.F.S. is a scientific advisor to Pfizer. None of these companies influenced the design of the study, the interpretation of the data, the amount of data reported, or financially profit by publication of these pre-competitive results. The other authors do not report conflicts of interest.

Department of Psychiatry, Harvard Medical School, Boston, MA, USA <sup>13</sup> FMRIB Centre, University of Oxford, United Kingdom <sup>14</sup> Department of Statistics & WMG, University of Warwick, Coventry, United Kingdom <sup>15</sup> Departments of Psychiatry & Human Genetics, Virginia Commonwealth University, Richmond, VA, USA <sup>16</sup> Division of Psychiatry, Royal Edinburgh Hospital, Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, United Kingdom <sup>17</sup> Intramural Research Program, National Institutes of Health, US Dept of Health & Human Services, Bethesda, USA <sup>18</sup> Central Institute of Mental Health, Medical Faculty Mannheim, University Heidelberg, Mannheim, Germany <sup>19</sup> Department of Biomedicine, Aarhus University, Aarhus, Denmark <sup>20</sup> The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Aarhus and Copenhagen, Denmark <sup>21</sup> Center for integrated Sequencing, iSEQ, Aarhus University, Aarhus, Denmark <sup>22</sup> NORMENT - KG Jebsen Centre, Institute of Clinical Medicine, University of Oslo, Oslo, Norway <sup>23</sup> Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway <sup>24</sup> Center for Translational Research in Systems Neuroscience and Psychiatry, Department of Psychiatry and Psychotherapy, University Medical Center, Goettingen, Germany <sup>25</sup> Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales (UNSW), Sydney, Australia <sup>26</sup> Neuropsychiatric Institute, Prince of Wales Hospital, Sydney, Australia <sup>27</sup> Department of Psychiatry, University Hospital Marqués de Valdecilla, School of Medicine, University of Cantabria-IDIVAL, Santander, Spain <sup>28</sup> Cibersam (Centro Investigación Biomédica en Red Salud Mental), Madrid, Spain <sup>29</sup> Center for Neuroimaging, Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, USA <sup>30</sup> Indiana Alzheimer Disease Center, Indiana University School of Medicine, Indianapolis, USA <sup>31</sup> Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, USA <sup>32</sup> Department of Child and Adolescent Psychiatry, Faculty of Medicine and University Hospital, TU Dresden, Dresden, Germany <sup>33</sup> Georgia State University, Atlanta, USA <sup>34</sup> Mind Research Network, Albuquerque, NM, USA <sup>35</sup> QIMR Berghofer Medical Research Institute, Brisbane, Australia <sup>36</sup> School of Psychology, University of Queensland, Brisbane, Australia <sup>39</sup> MRC Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, UK <sup>40</sup> National Centre for Mental Health, Cardiff University, Cardiff, UK <sup>41</sup> Medical and Population Genetics Program, Broad Institute of MIT and Harvard, Cambridge, MA, USA <sup>42</sup> Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden <sup>43</sup> Department of Genetics, University of North Carolina, Chapel Hill, NC, USA <sup>44</sup> Department of Psychiatry, University of North Carolina, Chapel Hill, NC, USA

# These authors contributed equally to this work.

## Abstract

Schizophrenia is a devastating psychiatric illness with high heritability. Brain structure and function differ, on average, between schizophrenia cases and healthy individuals. As common genetic associations are emerging for both schizophrenia and brain imaging phenotypes, we can now use genome-wide data to investigate genetic overlap. Here we integrated results from common variant studies of schizophrenia (33,636 cases, 43,008 controls) and volumes of several (mainly subcortical) brain structures (11,840 subjects). We did not find evidence of genetic overlap between schizophrenia risk and subcortical volume measures either at the level of common variant

genetic architecture or for single genetic markers. The current study provides proof-of-concept (albeit based on a limited set of structural brain measures), and defines a roadmap for future studies investigating the genetic covariance between structural/functional brain phenotypes and risk for psychiatric disorders.

## Keywords

schizophrenia; MRI; brain imaging; genetics; GWAS; meta-analysis; endophenotype

## Introduction

Schizophrenia is a devastating, highly heritable psychiatric disorder that affects approximately 1% of the population.<sup>1</sup> Despite marked recent successes in identifying genetic risk factors and pathways involved in schizophrenia,<sup>1-4</sup> the neurobiology of schizophrenia remains poorly understood.

Many differences in brain function and structure have been reported in cases with schizophrenia compared with controls, although there is considerable inter-individual heterogeneity. Of specific relevance to this study, a recent meta-analysis found that schizophrenia cases had smaller hippocampus, amygdala, thalamus, nucleus accumbens, and intracranial volumes along with larger pallidum and lateral ventricle volumes.<sup>5,6</sup> Hippocampal and lateral ventricle volumes were influenced by antipsychotic medication use.<sup>5</sup> In addition, mean hippocampal volume is smaller in high-risk individuals and in unaffected first-degree relatives of schizophrenia cases.<sup>7,8</sup>

Structural brain measurements, such as those from magnetic resonance imaging (MRI), typically have high reproducibility and low measurement error and can be highly heritable.<sup>9,10</sup> Increasingly large studies of brain morphometry are being performed, and are being used to evaluate the effects of common and rare genetic contributions on brain structure.<sup>9,11</sup>

With genome-wide association results available from large samples for schizophrenia and for MRI-based brain phenotypes, we can now use genomic approaches to evaluate the genetic link between disease risk and such brain measures. Findings of covariation would help us develop new hypotheses about the structures involved in the primary disease process of schizophrenia. In this proof-of-concept study, we created a roadmap for the analysis of genetic covariation using a battery of complementary methods. We evaluated the overlap of common genetic variation at the high level of genetic architecture as well as of individual genetic variants. We also evaluated common genetic variant effect sizes on neuroimaging phenotypes and schizophrenia. The data we analyzed are from large mega-analyses by the PGC (Psychiatric Genomics Consortium) for schizophrenia<sup>3</sup> and meta-analyses from the ENIGMA consortium (Enhancing NeuroImaging Genetics through Meta-Analysis) for eight MRI volumetric measures (amygdala, caudate nucleus, hippocampus, nucleus accumbens, pallidum, putamen, thalamus, and intracranial volume (ICV)).<sup>9</sup> Our results suggest that common genetic variation predisposing to schizophrenia does not show evidence of overlap

with common genetic variation influencing these eight brain structure volumes. Genetic effect sizes did not differ significantly for neuroimaging and schizophrenia phenotypes.

## Results

We analyzed genome-wide association data for schizophrenia (33,636 cases and 43,008 controls) and eight structural MRI brain measures (11,840 individuals). Sample characteristics are presented in *Supplementary Table 1*. These data were used for a comprehensive set of comparisons of common variant genetic sharing between schizophrenia and brain volumetric measures.

### Comparisons of common variant genetic architectures

**Linkage disequilibrium score regression (LDSR)**<sup>12</sup>—Using GWA summary statistics (excluding the extended MHC region), we used LDSR<sup>12</sup> to estimate the heritability of schizophrenia due to common SNPs at 25.5% (SE=1.1%) along with eight brain volumetric measures (*Table 1*). The SNP-based heritability estimates for the MRI measures ranged from 11% (nucleus accumbens) to 30% (putamen). The heritability for amygdala volume was non-significant in this sample. The genetic correlations of MRI volumetric measures with schizophrenia were all non-significant (*Table 1*). These negative findings stand in contrast to the relatively high common-variant correlations of schizophrenia with bipolar disorder and major depressive disorder.<sup>13,14</sup>

**Genetic predisposition scores**—In the genetic “risk” score approach,<sup>15</sup> we considered the ENIGMA GWA results as “training” sets in order to compute common variant genetic predisposition to (for instance) greater ICV for each schizophrenia case and control. We then compared the mean polygenic predisposition score in cases to that in controls. None of the correlations was significant after correction for eight comparisons (*Figure 1* and *Table 2*). The strongest effect (for hippocampal volume) was almost entirely driven by one SNP (rs2268894),<sup>9</sup> but only three SNPs met the p-value threshold of  $1 \times 10^{-6}$  for inclusion in this analysis. These null results are in contrast to the robust evidence for common variant genetic correlations between schizophrenia and other psychiatric disorders.<sup>16</sup>

**Rank-rank hypergeometric overlap test (RRHO)**<sup>17</sup>—We quantified overlap between pairs of GWA results ranked by their association statistics using RRHO based on 172,652 SNPs. The overlap of rank-ordered lists of genetic variants influencing any of the brain MRI volumes and those conferring risk for schizophrenia was not statistically significant (*Figure 2*). The overlap between genetic contributions to putamen and caudate nucleus volumes was used as a positive control; the overlap between genetic contributions to hippocampal volume and the presumably unrelated trait of thumb whorl structure<sup>18</sup> was used as a negative control. The latter comparison showed similar overlap to that of brain structure and schizophrenia.

### Sign tests

We compared the pattern of GWA results by checking whether the signs of the regression coefficients<sup>3</sup> were consistently in the same direction between the top associations for

schizophrenia and those for the MRI volumetric measures. None of the sign tests showed consistent directions of effect (*Table 3*).

### Analysis of single genetic variants

**Genome-wide significant associations**—We evaluated the 128 genome-wide significant schizophrenia index SNPs<sup>3</sup> for association with brain volumes.<sup>9</sup> One association survived correction for 876 comparisons: rs2909457\*A (chr2:162,845,855, intergenic between *SLC4A10* and *DPP4*) was associated with decreased hippocampal volume ( $P=1.2\times 10^{-6}$ , effect size= $-23\text{ mm}^3$  per allele) and decreased risk for schizophrenia (odds ratio=0.94,  $P=4.6\times 10^{-8}$ ). However, this finding was in the opposite direction of expectations given previous observations of smaller hippocampal volumes in cases relative to controls (*Supplementary Table 2*).<sup>6</sup> Starting with the eight SNPs previously found associated with the brain volumes,<sup>9</sup> no significant associations with schizophrenia were observed (*Supplementary Table 2*).

**SNP meta-analyses**—We also performed GWA meta-analyses of the schizophrenia and brain structure results. The Manhattan plots for these analyses are shown in *Supplementary Figures 1-8*. In *Supplementary Table 3*, the genome-wide significant findings are given. In most instances, the results were entirely driven by the association with schizophrenia.

**Conjunction analysis**—To identify individual SNPs that influence risk for both schizophrenia and brain structure, we implemented a conjunction test.<sup>19</sup> No SNP showed genome-wide significant association with both schizophrenia and brain structure, although several loci were detected at sub-threshold levels (*Supplementary Figure 9*).

### Comparison of genetic effect sizes for clinical and brain volume measures

Some investigators have suggested that common genetic variants underlying continuous brain imaging endophenotypes may have larger effect sizes than those for neuropsychiatric disorders (e.g., schizophrenia).<sup>20,22</sup> To test this hypothesis, we compared the maximum effect sizes from replicated genetic associations for each trait. For comparability across quantitative or binary traits, effect sizes were assessed as percent of variance explained (for MRI volumes) or percent of variance explained on the liability scale (for schizophrenia).<sup>23</sup> As shown in *Supplementary Figure 10*, individual common variants had only a small influence on either brain structure or schizophrenia. Effect sizes for individual SNPs were similar for both brain structure and schizophrenia, and of the same order as those observed for anthropometric traits such as height.<sup>24</sup>

### Discussion

In this proof-of-concept study, we evaluated the relationship between common genetic variants implicated in schizophrenia and those associated with subcortical brain volumes and ICV. The sample sizes were the largest yet applied to these questions. With a comprehensive set of analyses, we did not find evidence for notable genetic correlations, either at a high level (i.e., common variant genetic architecture) or for single genetic markers. Our findings do not support the hypothesis that these subcortical brain volume measures and ICV are



causally associated with schizophrenia risk. Similarly, we did not find evidence that common SNPs have pleiotropic effects on these MRI volumes and schizophrenia. Our results suggest alternative hypotheses that require consideration and refutation – that the volumetric differences observed in schizophrenia cases may be epiphenomena unrelated to its primary genetic causes, a result of prenatal environment, or result from reverse causation.<sup>25</sup> Finally, the effect sizes of SNPs implicated in schizophrenia and those associated with brain volumes were broadly similar.

We studied a limited set of brain MRI measures. Our study should be considered a proof-of-concept for evaluating genetic covariation rather than decisively addressing the full range of hypotheses pertaining to the genetic overlap of brain imaging measures with neuropsychiatric disease risk. We provide a rigorous roadmap for more definitive and larger future studies. Full elucidation of the brain correlates of schizophrenia will require a fuller set of structural and functional imaging measures (perhaps at the voxel level) along with evaluation of common and rare genetic variation.

The null findings of this study should be interpreted in light of several qualifiers. First, several brain regions that are not expected *a priori* to overlap with schizophrenia were included for completeness (e.g., caudate and putamen volumes are uncorrelated with schizophrenia,<sup>5,6</sup> and amygdala volume did not have SNP-heritability different from zero in our study). Second, other neuroimaging phenotypes could be more informative for schizophrenia (e.g., cortical thickness, ventricular volume, diffusion tensor imaging, or functional activity).<sup>26,27</sup> Indeed, genetic variants associated with disease may influence distinct cell types within circumscribed neural circuits that may not be captured by MRI. Third, the ENIGMA MRI protocol served to harmonize images obtained from different scanners and protocols. While we have shown this performs well, genetic signal might have been lessened. Fourth, in this study of adults, we may not have observed the brain regions at the most appropriate time for identifying genetic overlap with schizophrenia, given that the volumes of most subcortical brain structures plateau in late adolescence to early adulthood. While schizophrenia is widely believed to be a neurodevelopmental disorder,<sup>28</sup> its onset generally follows the period of greatest growth for these structures. Fifth, relatively small genetic correlations between schizophrenia and these brain volumes may have been masked by combining datasets in a meta-analytic framework (e.g., heterogeneous sample characteristics such as age, sex, and technical noise resulting from different MRI scanners or acquisition sequences may remain). It is conceivable that this resulted in the lower than expected SNP-heritability for some of these measures. Mega-analysis could be an important way to improve control for heterogeneity. Sixth, we evaluated only common genetic variation. Although common genetic variation explains far more of the risk for schizophrenia than rare copy number variation or rare deleterious exonic variation,<sup>2</sup> rare genetic effects on brain structure could be salient for some cases of schizophrenia. Finally, the sample sizes and statistical power of the schizophrenia and neuroimaging data sets differed. The PGC has attained a sample size sufficient to detect many common loci of small effect, whereas ENIGMA is earlier in the discovery arc.<sup>29</sup>

Brain volume heritability estimates from genome-wide data obtained using LDSR<sup>14</sup> were lower than observed in previous studies.<sup>30</sup> This was expected for the subcortical regions, as

those were corrected for ICV. For ICV, a likely source of difference with previous studies is the removal of the extended MHC region from our analysis.

Although we found no evidence for genetic correlation between subcortical volumes and schizophrenia, we also investigated whether effect sizes of genetic variants are larger for brain measures than for schizophrenia. This point has been debated with respect to “endophenotype” studies, which attempt to identify quantifiable brain measures or other biomarkers thought to be intermediate between genotype and the liability to a disorder.<sup>31,33</sup> An endophenotype that lies on a causal pathway to a clinical disorder could increase power for genetic studies. Prior studies addressed this hypothesis in far smaller samples. We compared SNP effect sizes for the top findings for schizophrenia with those for subcortical volumes (hippocampus, putamen, caudate) and ICV. The results of this analysis showed similar effect sizes. Importantly, the endophenotype concept is unlikely to be sufficiently addressed in these analyses given the reasons noted above.

In conclusion, this paper presents a roadmap for comprehensive evaluation of genetic covariation between neuropsychiatric disease liability and brain imaging measures. The current analysis was limited to a small number of brain volume phenotypes, and no evidence of genetic overlap was identified. More extensive brain-wide and genome-wide analyses may help in the mechanistic dissection of genetic risk for disease.

## Online Methods

A supplementary methods checklist is available. The data used for the analyses described here are available to researchers. The ENIGMA data can be obtained from <http://enigma.ini.usc.edu/enigma-vis>. The PGC data can be downloaded from <http://www.med.unc.edu/pgc/downloads>.

## PGC schizophrenia

We mega-analyzed individual genotype data from 46 European-ancestry schizophrenia GWAS datasets (full details in reference<sup>3</sup>). Briefly, quality control and imputation were performed by the PGC Statistical Analysis Group for each dataset separately. Genotype imputation was with the pre-phasing/imputation stepwise approach implemented in IMPUTE2/SHAPEIT (chunk size of 3 Mb and default parameters) using the 1000 Genomes Project dataset (phase 1, August 2012, URLs). After imputation, we identified autosomal SNPs with high imputation accuracy across all samples. For robust relatedness testing and population structure analysis, we evaluated a subset of SNPs following LD-pruning ( $r^2 > 0.02$ ) and frequency filtering ( $MAF > 0.05$ ). For association testing, we evaluated the 46 datasets separately using an additive logistic regression model including ancestry principal components as covariates, and then conducted a meta-analysis of the 52 sets of results using an inverse-weighted fixed effects model. After excluding subjects who were also in ENIGMA ( $N=458$ , see below), 33,636 cases and 43,008 controls were used for calculations (*Supplementary Table 1*).



## ENIGMA, sample with brain volume measures and assessment of endophenotype

The data analyzed here are from the ENIGMA analysis of eight MRI volumetric measures (full details in reference<sup>9</sup>). MRI brain scans and genome-wide genotype data were available for 11,840 subjects from 22 cohorts (*Supplementary Table 1*). Only cohorts without schizophrenia cases and controls overlapping with the PGC schizophrenia samples were included. Participants clustered with subjects of known European ancestry as verified by multidimensional scaling (MDS) analysis. Genomic data were imputed to a reference panel (1000 Genomes, v3 phase1) comprising only European samples and with monomorphic SNPs removed. Imputation was performed at each site using MaCH for phasing and minimac for imputation.<sup>34</sup> Only SNPs with an imputation score of RSQ > 0.5 and minor allele counts > 10 within each site were included. Tests of association were conducted separately for eight MRI volumetric phenotypes (nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen, thalamus, and ICV) with the following covariates in a multiple linear regression framework: age, age<sup>2</sup>, sex, 4 MDS components (to account for population structure), ICV (for subcortical brain phenotypes), and diagnosis (when applicable). The GWA statistics from each of the 22 sites were combined using a fixed-effect inverse variance-weighted meta-analysis as implemented in METAL.<sup>35</sup>

## Removal of duplicated individuals

Subject overlap between all PGC and ENIGMA cohorts was evaluated using a checksum algorithm in order to ensure the robustness of our results given that some analyses were sensitive to the presence of duplicate individuals. For each individual, ten checksum numbers were created based on ten batches of 50 SNP genotypes and compared between individuals from both consortia. Based on these comparisons and a general exclusion of cohorts containing schizophrenia cases, 1,517 individuals were removed from ENIGMA and 458 subjects were removed from the PGC.

## Linkage disequilibrium score regression (LDSR)

For LDSR, each dataset underwent additional filtering. Only markers overlapping with HapMap Project Phase 3 SNPs and passing the following filters were included: INFO score > 0.9 (where available), study missingness of 0, and MAF > 1%. Indels and strand-ambiguous SNPs were removed. To remove a potential source of bias, all SNPs in the extended MHC region (chr6:25-35 Mb) were removed from all datasets. The schizophrenia analysis included only results from European studies were used (LDSR requires LD data from a comparable sample). For the ENIGMA amygdala results, the mean  $X^2$  was too low (1.0051) to reliably estimate heritability using LDSR.

The analysis was conducted using a two-step procedure with the LD-scoring analysis package.<sup>12,14</sup> An unconstrained regression was run to estimate the regression intercepts for each phenotype, followed by an analysis with regression intercepts constrained to those estimated in the first step and the covariance intercept defined as zero (note that we took steps to exclude overlapping samples). Standard errors were estimated using a block jackknife procedure and used to calculate *P*-values.

## Genetic predisposition analyses

To investigate the combined impact of ENIGMA association results on case-control status in the PGC schizophrenia data, we performed a series of genetic predisposition score analyses. For each ENIGMA volumetric phenotypes, we excluded SNPs with MAF <2%, indels, and SNPs in the extended MHC region (chr6:25-34 Mb). We then “clumped” the data, discarding variants within 500 kb of and in  $r^2 \geq 0.1$  with another more significant marker. We performed genetic predisposition score prediction of target subgroups as originally described<sup>15</sup> for several  $P$ -value thresholds ( $5 \times 10^{-8}$ ,  $1 \times 10^{-6}$ ,  $1 \times 10^{-4}$ , 0.001, 0.01, 0.05, 0.1, 0.2, 0.5, 1.0), multiplying the effect size of the ENIGMA phenotype of each variant by the imputation probability for the risk allele in each individual. The resulting values were summed so that each individual had a genetic predisposition score for further analyses. Two outcome variables are reported in **Table 2**: the significance of the case-control score difference analyzed by logistic regression (including ancestry-based principal components and a study indicator as covariates) and the proportion of variance explained (Nagelkerke's  $R^2$ ) computed by comparison of a full model (covariates + polygenic risk scores) score to a reduced model (covariates only). Note that these  $R^2$  estimates are biased due to recruitment of the case-control studies and as the numbers of cases and controls do not reflect the underlying risk of disease in the population.

## Rank-rank-hypergeometric overlap test (RRHO)

RRHO<sup>17</sup> tests the hypothesis that ordering of two lists (LD-pruned GWAS results for schizophrenia versus a brain structure phenotype) by the strength of their association is arbitrary. The number of independent SNPs in common between the two ordered lists is evaluated at specified step sizes. Two lists that show similar ordering of SNPs demonstrate a global pattern of similarity of associations. Independent SNPs were selected based on the 1000 Genomes European dataset for 200 SNP windows shifted at five SNP intervals using an  $r^2$  threshold of 0.25. SNPs found in both PGC and ENIGMA data with MAF  $\geq 0.01$  were retained (172,652 SNPs). The SNPs were then ordered by the  $-\log_{10}(\text{p-value})$  of association multiplied by the effect size. A two-sided RRHO test that allowed testing for either over- or under-enrichment was used with a step-size of 3000 SNPs.

## Finger whorl data used as control in conjunction analysis

A GWAS of a dermatoglyphic trait (presence of a whorl on the left thumb), collected as part of an ongoing study at the Queensland Institute of Medical Research,<sup>18</sup> was used to provide a negative control for the RRHO test. Briefly, rolled ink prints were collected on archival quality paper, and fingerprint patterns were manually coded. Complete data from 3,314 participants (twins and their family members) were available. Genotypes were imputed to the 1000 Genomes Project reference (phase 1 version 3). GWAS was conducted using Merlin-offline to account for relatedness and zygosity.

## Lookup of top GWAS SNP findings

Evidence for an effect of the reported 128 independent schizophrenia-associated SNPs on subcortical brain volumes and ICV was studied through a look-up of results. rs115329265 was not available in the ENIGMA data and was replaced by a SNP in moderate LD

(chr6:28305863R;  $r^2=0.64$ ); rs77149735 was not available in ENIGMA and could not be replaced by a SNP in LD. Three chrX SNPs (rs1378559, rs5937157, and rs12845396) were excluded, because chrX data were not available from ENIGMA. Effects of the eight independent SNPs associated with brain volumes reported by ENIGMA on schizophrenia risk were studied through a look-up of results in the PGC data.

Multiple comparison correction was performed by estimating the effective number of independent tests ( $M_{\text{eff}}$ ). This method considers the correlation structure (**Supplementary Table 4**) between brain measures and calculates the  $M_{\text{eff}}$  based on the observed eigenvalue variance of the different brain volume measures using matSpD (see URLs). The p-value for significance was 0.05 divided by the sum of (a)  $M_{\text{eff}}$  times the number of SNPs included in the lookup from PGC to ENIGMA ( $n=124$ ), and (b) the number of SNPs included in the lookup from ENIGMA to PGC ( $n=8$ ). Eight brain volumes resulted in seven independent tests, and only SNPs with a  $P < 5.7 \times 10^{-5}$  were considered significant.

### SNP sign test in the top GWAS findings

To investigate a potential accumulation of same or opposite direction effects of SNPs between PGC schizophrenia and ENIGMA, we counted the number of same direction effects for the top-findings from the schizophrenia dataset (94 LD-independent genome-wide significant SNPs, 231 with  $P < 1 \times 10^{-6}$ ) in the different brain structure datasets and tested the significance of the result in a binomial test ( $n=14$  tests for 7 effective ENIGMA phenotypes and 2  $P$ -value thresholds).

### Conjunction analysis

To determine whether a particular SNP is linked to both brain structure and risk for schizophrenia, a conjunction analysis was used.<sup>19</sup> This analysis makes inference on the alternative hypothesis that both null hypotheses are false. This is in distinction to a traditional meta-analysis method which infers on an alternative hypothesis that one or more null hypotheses are false. A conjunction analysis is calculated as:  $P_{\text{conj}} = \max(P_{\text{brain}}, P_{\text{case-control}})$ , where  $P_{\text{brain}}$  is the significance of the SNP associated to brain structure and  $P_{\text{case-control}}$  is the significance of the SNP association to schizophrenia. As conjunction tests can be very conservative, an adjustment to this test<sup>36</sup> based on the estimated fraction of false nulls was used here with modifications ( $P'_{\text{conj}}$ ). Over 7.5 million SNPs found in both the ENIGMA and PGC datasets with MAF  $> 0.01$  were evaluated.

A conjunction null hypothesis is the union of the individual null hypotheses, producing a ‘composite null hypothesis’. In standard testing situations a “point null hypothesis” is used, meaning that there is exactly one configuration of the unknown parameters of interest that corresponds to the null. For example, “no gene-brain association, no case-control association” is a point null hypothesis. A composite null has multiple configurations. For example, both of these configurations fall into the conjunction null hypothesis: “true gene-brain association, no case-control association”; “no gene-brain association; true case-control association”. A valid conjunction test has to control false positive risk over all possible configurations in the conjunction null. Put another way, a conjunction test has to be

calibrated for the worst possible configuration of true signals, and as a result can be quite conservative when the true state of the model is not one of the extreme cases.

The method of Deng et al.<sup>36</sup> attempts to reduce the conservativeness of the conjunction procedure in the multiple testing setting. The authors propose a method that estimates prevalence of null hypotheses in each of the individual tests being combined. With this information, a “relaxed” test can be constructed that is less conservative. However, a crucial equation in that paper is in error. The equation below provides the estimator for the proportion of false null hypothesis for each of the two tests to be combined. The expression is based on the method of Storey<sup>37</sup>, who posed it as an estimate of the proportion of *true* null hypotheses. Deng et al.<sup>36</sup> apparently inverted the result incorrectly; the correct expression is:

$$\hat{\pi}_i(\lambda) = 1 - \frac{\#\{p_i(j) > \lambda\}}{(1 - \lambda)n}$$

In our analyses, the  $\lambda$  parameter in the equation above was set to 0.25.

### SNP meta-analysis

We combined the association *P*-values of SNPs associated with schizophrenia with SNPs associated with the seven subcortical brain volumes and ICV from ENIGMA. Using METAL,<sup>35</sup> we conducted a sample size-weighted meta-analysis for schizophrenia (effective sample size 71,715) and ENIGMA (variable sample sizes per SNP ranging from 8,000-11,000). SNPs were excluded if they were not present in both datasets and for MAF < 1% (per analysis). The total number of SNPs present in the eight meta-analyses ranged from 7,847,762 to 7,945,194.

### SNP effect size comparisons

SNP effect sizes were extracted from studies of brain structure (ENIGMA),<sup>9</sup> schizophrenia (PGC),<sup>3</sup> height (GIANT),<sup>24</sup> and educational attainment (EduYears).<sup>38</sup> The five highest effect size SNPs were selected for schizophrenia and height, all genome-wide significant SNPs were displayed for brain structure volumes and EduYears. Percent variance was calculated on the liability scale for schizophrenia for comparison with quantitative traits.<sup>23</sup> For brain structures, height, and EduYears, percent variance explained was calculated as  $R^2_{\text{glc}}/(1-R^2_{\text{c}}) = (t^2/((n-k-1)+t^2))*100$ , where the *t*-statistic is calculated as the  $\beta$ -coefficient for a given SNP from the regression model (controlling for covariates) divided by the standard error of the  $\beta$ -estimate, *n* is the total number of subjects, and *k* is the total number of covariates. 95% confidence intervals were calculated by transforming percent variance explained to a *Z*-statistic using Fisher's *Z* transformation, finding the 95% confidence intervals of the *Z*-statistic, and transforming this interval back into percent variance explained.

### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## PGC-SCZ consortium collaborators include

Stephan Ripke<sup>1,7,8,9</sup>, Benjamin M Neale<sup>7,8,11,38,41</sup>, Aiden Corvin<sup>45</sup>, James TR Walters<sup>39</sup>, Kai-How Farh<sup>7</sup>, Peter A Holmans<sup>39,40</sup>, Phil Lee<sup>8,11,12</sup>, Brendan Bulik-Sullivan<sup>7,8</sup>, David A Collier<sup>46,47</sup>, Hailiang Huang<sup>7,41</sup>, Tune H Pers<sup>41</sup>, Ingrid Agartz<sup>48,49,50</sup>, Esben Agerbo<sup>20</sup>, Margot Albus<sup>51</sup>, Madeline Alexander<sup>52</sup>, Farooq Amin<sup>53,54</sup>, Silviu A Bacanu<sup>55</sup>, Martin Begemann<sup>56</sup>, Richard A Belliveau Jr<sup>8</sup>, Judit Bene<sup>57,58</sup>, Sarah E Bergen<sup>8,42</sup>, Elizabeth Bevilacqua<sup>8</sup>, Tim B Bigdeli<sup>55</sup>, Donald W Black<sup>59</sup>, Richard Bruggeman<sup>60</sup>, Nancy G Buccola<sup>61</sup>, Randy L Buckner<sup>62,63,64</sup>, William Byerley<sup>65</sup>, Wiepke Cahn<sup>66</sup>, Guiqing Cai<sup>67,68</sup>, Murray J Cairns<sup>69,70,71</sup>, Dominique Campion<sup>72</sup>, Rita M Cantor<sup>73</sup>, Vaughan J Carr<sup>69,74</sup>, Noa Carrera<sup>39</sup>, Stanley V Catts<sup>69,75</sup>, Kimberley D Chambert<sup>8</sup>, Raymond CK Chan<sup>76</sup>, Eric YH Chen<sup>77,78</sup>, Ronald YL Chen<sup>78</sup>, Wei Cheng<sup>79</sup>, Eric FC

Cheung <sup>80</sup>, Siow Ann Chong <sup>81</sup>, C Robert Cloninger <sup>82</sup>, David Cohen <sup>83</sup>, Nadine Cohen <sup>84</sup>, Paul Cormican <sup>45</sup>, Nick Craddock <sup>39,40</sup>, Benedicto Crespo-Facorro <sup>85,86</sup>, James J Crowley <sup>43</sup>, David Curtis <sup>87,88</sup>, Michael Davidson <sup>89</sup>, Kenneth L Davis <sup>67</sup>, Franziska Degenhardt <sup>90,91</sup>, Jorgen Del Favero <sup>92</sup>, Lynn E DeLisi <sup>12</sup>, Ditte Demontis <sup>20</sup>, Dimitris Dikeos <sup>93</sup>, Timothy Dinan <sup>94</sup>, Srdjan Djurovic <sup>48,95</sup>, Gary Donohoe <sup>45,96</sup>, Elodie Drapeau <sup>67</sup>, Jubao Duan <sup>97,98</sup>, Frank Dudbridge <sup>99</sup>, Peter Eichhammer <sup>100</sup>, Johan Eriksson <sup>101,102,103</sup>, Valentina Escott-Price <sup>39</sup>, Laurent Essioux <sup>104</sup>, Ayman H Fanous <sup>105,106,107,108</sup>, Martilias S Farrell <sup>43</sup>, Josef Frank <sup>109</sup>, Lude Franke <sup>110</sup>, Robert Freedman <sup>111</sup>, Nelson B Freimer <sup>112</sup>, Joseph I Friedman <sup>67</sup>, Menachem Fromer <sup>7,8,11</sup>, Giulio Genovese <sup>8</sup>, Lyudmila Georgieva <sup>39</sup>, Elliot S Gershon <sup>113</sup>, Ina Giegling <sup>114,115</sup>, Paola Giusti-Rodríguez <sup>43</sup>, Stephanie Godard <sup>116</sup>, Jacqueline I Goldstein <sup>7,41</sup>, Srihari Gopal <sup>117</sup>, Jacob Gratten <sup>118</sup>, Lieuwe de Haan <sup>119</sup>, Christian Hammer <sup>56</sup>, Marian L Hamshere <sup>39</sup>, Mark Hansen <sup>120</sup>, Thomas Hansen <sup>20</sup>, Vahram Haroutunian <sup>67,121,122</sup>, Annette M Hartmann <sup>114</sup>, Frans A Henskens <sup>69,123,124</sup>, Stefan Herms <sup>90,91,125</sup>, Joel N Hirschhorn <sup>41</sup>, Per Hoffmann <sup>90,91,125</sup>, Andrea Hofman <sup>90,91</sup>, Mads V Hollegaard <sup>126</sup>, David M Hougaard <sup>126</sup>, Masashi Ikeda <sup>127</sup>, Inge Joa <sup>128</sup>, Antonio Julià <sup>129</sup>, Anna K Kähler <sup>42</sup>, René S Kahn <sup>66</sup>, Luba Kalaydjieva <sup>130,131</sup>, Sena Karachanak-Yankova <sup>132</sup>, Juha Karjalainen <sup>110</sup>, David Kavanagh <sup>39</sup>, Matthew C Keller <sup>133</sup>, Brian J Kelly <sup>70</sup>, James L Kennedy <sup>134,135,136</sup>, Andrey Khrunin <sup>137</sup>, Yunjung Kim <sup>43</sup>, Janis Klovins <sup>138</sup>, James A Knowles <sup>139</sup>, Bettina Konte <sup>114</sup>, Vaidutis Kucinskas <sup>140</sup>, Zita Ausrele Kucinskiene <sup>140</sup>, Hana Kuzelova-Ptackova <sup>141</sup>, Claudine Laurent <sup>52,142</sup>, S Hong Lee <sup>118</sup>, Jimmy Lee Chee Keong <sup>81,143</sup>, Sophie E Legge <sup>39</sup>, Bernard Lerer <sup>144</sup>, Miaoxin Li <sup>77,78,145</sup>, Tao Li <sup>146</sup>, Kung-Yee Liang <sup>147</sup>, Jeffrey Lieberman <sup>148</sup>, Svetlana Limborska <sup>137</sup>, Jouko Lönnqvist <sup>149</sup>, Carmel M Loughland <sup>69,70</sup>, Jan Lubinski <sup>150</sup>, Milan Macek Jr <sup>151</sup>, Patrik KE Magnusson <sup>42</sup>, Brion S Maher <sup>152</sup>, Wolfgang Maier <sup>153</sup>, Jacques Mallet <sup>154</sup>, Sara Marsal <sup>129</sup>, Manuel Mattheisen <sup>19,20,21</sup>, Morten Mattingsdal <sup>48,155</sup>, Robert W McCarley <sup>12</sup>, Colm McDonald <sup>156</sup>, Andrew M McIntosh <sup>16</sup>, Sandra Meier <sup>157</sup>, Carin J Meijer <sup>119</sup>, Bela Melegh <sup>57,58</sup>, Ingrid Melle <sup>23</sup>, Raquelle I Mesholam-Gately <sup>12</sup>, Andres Metspalu <sup>158</sup>, Patricia T Michie <sup>69,159</sup>, Lili Milani <sup>158</sup>, Vihra Milanova <sup>160</sup>, Younes Mokrab <sup>161</sup>, Derek W Morris <sup>45,96</sup>, Ole Mors <sup>20</sup>, Bertram Müller-Myhsok <sup>162,163,164</sup>, Kieran C Murphy <sup>165</sup>, Robin M Murray <sup>166</sup>, Inez Myin-Germeys <sup>167</sup>, Mari Nelis <sup>158</sup>, Igor Nenadic <sup>168</sup>, Deborah A Nertney <sup>169</sup>, Gerald Nestadt <sup>170</sup>, Kristin K Nicodemus <sup>171</sup>, Liene Nikitina-Zake <sup>138</sup>, Laura Nisenbaum <sup>172</sup>, Annelie Nordin <sup>173</sup>, Eadbhard O'Callaghan <sup>174</sup>, Colm O'Dushlaine <sup>8</sup>, F Anthony O'Neill <sup>175</sup>, Sang-Yun Oh <sup>176</sup>, Ann Olincy <sup>111</sup>, Line Olsen <sup>20</sup>, Jim Van Os <sup>167,177</sup>, Christos Pantelis <sup>69,178</sup>, George N Papadimitriou <sup>93</sup>, Sergi Papiol <sup>56</sup>, Elena Parkhomenko <sup>67</sup>, Michele T Pato <sup>139</sup>, Tiina Paunio <sup>179,180</sup>, Psychosis Endophenotypes International Consortium <sup>181</sup>, Diana O Perkins <sup>44</sup>, Olli Pietiläinen <sup>179,182</sup>, Jonathan Pimm <sup>88</sup>, Andrew J Pocklington <sup>39</sup>, John Powell <sup>166</sup>, Alkes Price <sup>41</sup>, Ann E Pulver <sup>170</sup>, Shaun M Purcell <sup>183</sup>, Digby Quested <sup>184</sup>, Henrik B Rasmussen <sup>20</sup>, Abraham Reichenberg <sup>67</sup>, Mark A Reimers <sup>55</sup>, Alexander L Richards <sup>39,40</sup>, Joshua L Roffman <sup>63,64</sup>, Panos Roussos <sup>183,185</sup>, Douglas M Ruderfer <sup>39</sup>, Veikko Salomaa <sup>102</sup>, Alan R Sanders <sup>97,186</sup>, Ulrich Schall <sup>69,70</sup>, Christian R Schubert <sup>187</sup>, Thomas G Schulze <sup>109,188</sup>, Sibylle G Schwab <sup>189</sup>, Edward M Scolnick <sup>8</sup>, Rodney J Scott <sup>69,71,190</sup>, Larry J Seidman <sup>12</sup>, Jianxin Shi <sup>191</sup>, Jeremy M Silverman <sup>67,192</sup>, Kang Sim <sup>81</sup>, Petr Slominsky <sup>137</sup>, Jordan W Smoller <sup>8,11,12</sup>, Hon-Cheong So <sup>78</sup>, Erik Söderman <sup>50</sup>, Chris C A Spencer <sup>193</sup>, Eli A Stahl <sup>41</sup>, Elisabeth Stogmann <sup>194</sup>, Richard E Straub <sup>195</sup>, Eric Strengman <sup>66,196</sup>, Jana Strohmaier <sup>157</sup>, T Scott Stroup <sup>148</sup>, Mythily

Subramaniam<sup>81</sup>, Jaana Suvisaari<sup>149</sup>, Dragan M Svrakic<sup>82</sup>, Jin P Szatkiewicz<sup>43</sup>, Srinivas Thirumalai<sup>197</sup>, Draga Toncheva<sup>198</sup>, Paul A Tooney<sup>69,71,199</sup>, Juha Veijola<sup>200,201</sup>, John Waddington<sup>202</sup>, Dermot Walsh<sup>203</sup>, Dai Wang<sup>117</sup>, Qiang Wang<sup>204</sup>, Bradley T Webb<sup>55</sup>, Mark Weiser<sup>89</sup>, Dieter B Wildenauer<sup>205</sup>, Nigel M Williams<sup>39</sup>, Stephanie Williams<sup>43</sup>, Stephanie H Witt<sup>109</sup>, Aaron R Wolen<sup>55</sup>, Emily HM Wong<sup>78</sup>, Brandon K Wormley<sup>55</sup>, Jing Qin Wu<sup>69,71</sup>, Hualin Simon Xi<sup>206</sup>, Clement C Zai<sup>134,135</sup>, Xuebin Zheng<sup>207</sup>, Fritz Zimprich<sup>194</sup>, Naomi R Wray<sup>118</sup>, Peter M Visscher<sup>118</sup>, Wellcome Trust Case-Control Consortium 2<sup>208</sup>, Rolf Adolfsson<sup>173</sup>, Ole A Andreassen<sup>22,23</sup>, Douglas HR Blackwood<sup>209</sup>, Anders D Børghlum<sup>20</sup>, Elvira Bramon<sup>210</sup>, Joseph D Buxbaum<sup>67,68,122,211</sup>, Sven Cichon<sup>90,91,125,212</sup>, Ariel Darvasi<sup>213</sup>, Enrico Domenici<sup>214</sup>, Hannelore Ehrenreich<sup>56</sup>, Tõnu Esko<sup>41</sup>, Pablo V Gejman<sup>97,186</sup>, Michael Gill<sup>45</sup>, Hugh Gurling<sup>88</sup>, Christina M Hultman<sup>42</sup>, Nakao Iwata<sup>127</sup>, Assen V Jablensky<sup>69,215,216,217</sup>, Erik G Jönsson<sup>48,50</sup>, Kenneth S Kendler<sup>55</sup>, George Kirov<sup>39</sup>, Jo Knight<sup>134,135,136</sup>, Todd Lencz<sup>218,219,220</sup>, Douglas F Levinson<sup>52</sup>, Qingqin S Li<sup>117</sup>, Jianjun Liu<sup>207,221</sup>, Anil K Malhotra<sup>218,219,220</sup>, Steven A McCarroll<sup>8</sup>, Andrew McQuillin<sup>88</sup>, Jennifer L Moran<sup>8</sup>, Preben B Mortensen<sup>20</sup>, Bryan J Mowry<sup>169,222</sup>, Markus M Nöthen<sup>90,91</sup>, Roel A Ophoff<sup>66,73,112</sup>, Michael J Owen<sup>39,40</sup>, Aarno Palotie<sup>8,11</sup>, Carlos N Pato<sup>139</sup>, Tracey L Petryshen<sup>8,12</sup>, Danielle Posthuma<sup>223,224,225</sup>, Marcella Rietschel<sup>109</sup>, Brien P Riley<sup>55</sup>, Dan Rujescu<sup>114,115</sup>, Pak C Sham<sup>77,78,145</sup>, Pamela Sklar<sup>122,183,185</sup>, David St Clair<sup>226</sup>, Daniel R Weinberger<sup>195,227</sup>, Jens R Wendland<sup>187</sup>, Thomas Werge<sup>20</sup>, Mark J Daly<sup>7,8,41</sup>, Patrick F Sullivan<sup>38,42,43,44</sup>, Michael C O'Donovan<sup>38,39,40</sup>

45 Neuropsychiatric Genetics Research Group, Department of Psychiatry, Trinity College Dublin, Dublin 8, Ireland

46 Eli Lilly and Company Limited, Erl Wood Manor, Sunninghill Road, Windlesham, Surrey, GU20 6PH, UK

47 Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, SE5 8AF, UK

48 NORMENT, KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, 0424 Oslo, Norway

49 Department of Psychiatry, Diakonhjemmet Hospital, 0319 Oslo, Norway

50 Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institutet, SE-17176 Stockholm, Sweden

51 State Mental Hospital, 85540 Haar, Germany

52 Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California 94305, USA

53 Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, Georgia 30322, USA

54 Department of Psychiatry and Behavioral Sciences, Atlanta Veterans Affairs Medical Center, Atlanta, Georgia 30033, USA

55 Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA

56 Clinical Neuroscience, Max Planck Institute of Experimental Medicine, Göttingen 37075, Germany

57 Department of Medical Genetics, University of Pécs, Pécs H-7624, Hungary

58 Szentagothai Research Center, University of Pécs, Pécs H-7624, Hungary

59 Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, Iowa 52242, USA

60 University Medical Center Groningen, Department of Psychiatry, University of Groningen, NL-9700 RB, The Netherlands

61 School of Nursing, Louisiana State University Health Sciences Center, New Orleans, Louisiana 70112, USA

62 Center for Brain Science, Harvard University, Cambridge, Massachusetts 02138, USA

63 Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts 02114, USA

64 Athinoula A Martinos Center, Massachusetts General Hospital, Boston, Massachusetts 02129, USA

65 Department of Psychiatry, University of California at San Francisco, San Francisco, California, 94143 USA

66 University Medical Center Utrecht, Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, 3584 Utrecht, The Netherlands

67 Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA

68 Department of Human Genetics, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA

69 Schizophrenia Research Institute, Sydney NSW 2010, Australia

70 Priority Centre for Translational Neuroscience and Mental Health, University of Newcastle, Newcastle NSW 2300, Australia

71 School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan NSW 2308, Australia



72 Centre Hospitalier du Rouvray and INSERM U1079 Faculty of Medicine, 76301 Rouen, France

73 Department of Human Genetics, David Geffen School of Medicine, University of California, Los Angeles, California 90095, USA

74 School of Psychiatry, University of New South Wales, Sydney NSW 2031, Australia

75 Royal Brisbane and Women's Hospital, University of Queensland, Brisbane QLD 4072, Australia

76 Institute of Psychology, Chinese Academy of Science, Beijing 100101, China

77 State Key Laboratory for Brain and Cognitive Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China

78 Department of Psychiatry, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China

79 Department of Computer Science, University of North Carolina, Chapel Hill, North Carolina 27514, USA

80 Castle Peak Hospital, Hong Kong, China

81 Institute of Mental Health, Singapore 539747, Singapore

82 Department of Psychiatry, Washington University, St Louis, Missouri 63110, USA

83 Department of Child and Adolescent Psychiatry, Assistance Publique Hopitaux de Paris, Pierre and Marie Curie Faculty of Medicine and Institute for Intelligent Systems and Robotics, Paris, 75013, France

84 Blue Note Biosciences, Princeton, New Jersey 08540, USA

85 University Hospital Marques de Valdecilla, Instituto de Formacion e Investigacion Marques de Valdecilla, University of Cantabria, E-39008 Santander, Spain

86 Centro Investigacion Biomedica en Red Salud Mental, Madrid, Spain

87 Department of Psychological Medicine, Queen Mary University of London, London E1 1BB, UK

88 Molecular Psychiatry Laboratory, Division of Psychiatry, University College London, London WC1E 6JJ, UK

89 Sheba Medical Center, Tel Hashomer 52621, Israel

90 Institute of Human Genetics, University of Bonn, D-53127 Bonn, Germany

91 Department of Genomics, Life and Brain Center, D-53127 Bonn, Germany



- 92 Applied Molecular Genomics Unit, VIB Department of Molecular Genetics, University of Antwerp, B-2610 Antwerp, Belgium
- 93 First Department of Psychiatry, University of Athens Medical School, Athens 11528, Greece
- 94 Department of Psychiatry, University College Cork, Co Cork, Ireland
- 95 Department of Medical Genetics, Oslo University Hospital, 0424 Oslo, Norway
- 96 Cognitive Genetics and Therapy Group, School of Psychology and Discipline of Biochemistry, National University of Ireland Galway, Co Galway, Ireland
- 97 Department of Psychiatry and Behavioral Sciences, NorthShore University HealthSystem, Evanston, Illinois 60201, USA
- 98 Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, Illinois 60637,, USA
- 99 Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK
- 100 Department of Psychiatry, University of Regensburg, 93053 Regensburg, Germany
- 101 Folkhälsan Research Center, Helsinki, Finland, Biomedicum Helsinki 1, Haartmaninkatu 8, FI-00290, Helsinki, Finland
- 102 National Institute for Health and Welfare, PO BOX 30, FI-00271 Helsinki, Finland
- 103 Department of General Practice, Helsinki University Central Hospital, University of Helsinki PO BOX 20, Tukholmankatu 8 B, FI-00014, Helsinki, Finland
- 104 Translational Technologies and Bioinformatics, Pharma Research and Early Development, F Hoffmann-La Roche, CH-4070 Basel, Switzerland
- 105 Mental Health Service Line, Washington VA Medical Center, Washington DC 20422, USA
- 106 Department of Psychiatry, Georgetown University School of Medicine, Washington DC 20057, USA
- 107 Department of Psychiatry, Virginia Commonwealth University School of Medicine, Richmond, Virginia 23298, USA
- 108 Department of Psychiatry, Keck School of Medicine of the University of Southern California, Los Angeles, California 90033, USA
- 109 Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, D-68159 Mannheim, Germany

- 110 Department of Genetics, University of Groningen, University Medical Centre Groningen, 9700 RB Groningen, The Netherlands
- 111 Department of Psychiatry, University of Colorado Denver, Aurora, Colorado 80045, USA
- 112 Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, California 90095, USA
- 113 Departments of Psychiatry and Human Genetics, University of Chicago, Chicago, Illinois 60637 USA
- 114 Department of Psychiatry, University of Halle, 06112 Halle, Germany
- 115 Department of Psychiatry, University of Munich, 80336, Munich, Germany
- 116 Departments of Psychiatry and Human and Molecular Genetics, INSERM, Institut de Myologie, Hôpital de la Pitié-Salpêtrière, Paris, 75013, France
- 117 Neuroscience Therapeutic Area, Janssen Research and Development, Raritan, New Jersey 08869, USA
- 118 Queensland Brain Institute, The University of Queensland, Brisbane, QLD 4072, Australia
- 119 Academic Medical Centre University of Amsterdam, Department of Psychiatry, 1105 AZ Amsterdam, The Netherlands
- 120 Illumina, La Jolla, California, California 92122, USA
- 121 JJ Peters VA Medical Center, Bronx, New York, New York 10468, USA
- 122 Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA
- 123 School of Electrical Engineering and Computer Science, University of Newcastle, Newcastle NSW 2308, Australia
- 124 Priority Research Centre for Health Behaviour, University of Newcastle, Newcastle NSW 2308, Australia
- 125 Division of Medical Genetics, Department of Biomedicine, University of Basel, Basel, CH-4058, Switzerland
- 126 Section of Neonatal Screening and Hormones, Department of Clinical Biochemistry, Immunology and Genetics, Statens Serum Institut, Copenhagen, DK-2300, Denmark
- 127 Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Aichi, 470-1192, Japan

- 128 Regional Centre for Clinical Research in Psychosis, Department of Psychiatry, Stavanger University Hospital, 4011 Stavanger, Norway
- 129 Rheumatology Research Group, Vall d'Hebron Research Institute, Barcelona, 08035, Spain
- 130 Centre for Medical Research, The University of Western Australia, Perth, WA 6009, Australia
- 131 The Perkins Institute for Medical Research, The University of Western Australia, Perth, WA 6009, Australia
- 132 Department of Medical Genetics, Medical University, Sofia 1431, Bulgaria
- 133 Department of Psychology, University of Colorado Boulder, Boulder, Colorado 80309, USA
- 134 Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, M5T 1R8, Canada
- 135 Department of Psychiatry, University of Toronto, Toronto, Ontario, M5T 1R8, Canada
- 136 Institute of Medical Science, University of Toronto, Toronto, Ontario, M5S 1A8, Canada
- 137 Institute of Molecular Genetics, Russian Academy of Sciences, Moscow 123182, Russia
- 138 Latvian Biomedical Research and Study Centre, Riga, LV-1067, Latvia
- 139 Department of Psychiatry and Zilkha Neurogenetics Institute, Keck School of Medicine at University of Southern California, Los Angeles, California 90089, USA
- 140 Faculty of Medicine, Vilnius University, LT-01513 Vilnius, Lithuania
- 141 Department of Biology and Medical Genetics, 2nd Faculty of Medicine and University Hospital Motol, 150 06 Prague, Czech Republic
- 142 Department of Child and Adolescent Psychiatry, Pierre and Marie Curie Faculty of Medicine, Paris 75013, France
- 143 Duke-NUS Graduate Medical School, Singapore 169857, Singapore
- 144 Department of Psychiatry, Hadassah-Hebrew University Medical Center, Jerusalem 91120, Israel
- 145 Centre for Genomic Sciences, The University of Hong Kong, Hong Kong, China
- 146 Mental Health Centre and Psychiatric Laboratory, West China Hospital, Sichuan University, Chengdu, 610041, Sichuan, China

- 147 Department of Biostatistics, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland 21205, USA
- 148 Department of Psychiatry, Columbia University, New York, New York 10032, USA
- 149 Department of Mental Health and Substance Abuse Services; National Institute for Health and Welfare, PO BOX 30, FI-00271 Helsinki, Finland
- 150 Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University in Szczecin, 70-453 Szczecin, Poland
- 151 Department of Biology and Medical Genetics, 2nd Faculty of Medicine and University Hospital Motol, 150 06, Prague, Czech Republic
- 152 Department of Mental Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland 21205, USA
- 153 Department of Psychiatry, University of Bonn, D-53127 Bonn, Germany
- 154 Centre National de la Recherche Scientifique, Laboratoire de Génétique Moléculaire de la Neurotransmission et des Processus Neurodégénératifs, Hôpital de la Pitié Salpêtrière, 75013, Paris, France
- 155 Research Unit, Sørlandet Hospital, 4604 Kristiansand, Norway
- 156 Department of Psychiatry, National University of Ireland Galway, Co Galway, Ireland
- 157 Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, D-68159 Mannheim, Germany
- 158 Estonian Genome Center, University of Tartu, Tartu 50090, Estonia
- 159 School of Psychology, University of Newcastle, Newcastle NSW 2308, Australia
- 160 First Psychiatric Clinic, Medical University, Sofia 1431, Bulgaria
- 161 Eli Lilly and Company Limited, Erl Wood Manor, Sunninghill Road, Windlesham, Surrey, GU20 6PH UK
- 162 Max Planck Institute of Psychiatry, 80336 Munich, Germany
- 163 Institute of Translational Medicine, University of Liverpool, Liverpool L69 3BX, UK
- 164 Munich Cluster for Systems Neurology (SyNergy), 80336 Munich, Germany
- 165 Department of Psychiatry, Royal College of Surgeons in Ireland, Dublin 2, Ireland
- 166 King's College London, London SE5 8AF, UK

- 167 Maastricht University Medical Centre, South Limburg Mental Health Research and Teaching Network, EURON, 6229 HX Maastricht, The Netherlands
- 168 Department of Psychiatry and Psychotherapy, Jena University Hospital, 07743 Jena, Germany
- 169 Queensland Centre for Mental Health Research, University of Queensland, Brisbane QLD 4076, Australia
- 170 Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA
- 171 Department of Psychiatry, Trinity College Dublin, Dublin 2, Ireland
- 172 Eli Lilly and Company, Lilly Corporate Center, Indianapolis, 46285 Indiana, USA
- 173 Department of Clinical Sciences, Psychiatry, Umeå University, SE-901 87 Umeå, Sweden
- 174 DETECT Early Intervention Service for Psychosis, Blackrock, Co Dublin, Ireland
- 175 Centre for Public Health, Institute of Clinical Sciences, Queen's University Belfast, Belfast BT12 6AB, UK
- 176 Lawrence Berkeley National Laboratory, University of California at Berkeley, Berkeley, California 94720, USA
- 177 Institute of Psychiatry, King's College London, London SE5 8AF, UK
- 178 Melbourne Neuropsychiatry Centre, University of Melbourne & Melbourne Health, Melbourne VIC 3053, Australia
- 179 Public Health Genomics Unit, National Institute for Health and Welfare, PO BOX 30, FI-00271 Helsinki, Finland
- 180 Department of Psychiatry, University of Helsinki, PO BOX 590, FI-00029 HUS, Helsinki, Finland
- 181 PEIC
- 182 Institute for Molecular Medicine Finland, FIMM, University of Helsinki, PO BOX 20 FI-00014, Helsinki, Finland
- 183 Division of Psychiatric Genomics, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA
- 184 Department of Psychiatry, University of Oxford, Oxford, OX3 7JX, UK
- 185 Institute for Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA

- 186 Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, Illinois 60637, USA
- 187 PharmaTherapeutics Clinical Research, Pfizer Worldwide Research and Development, Cambridge, Massachusetts 02139, USA
- 188 Department of Psychiatry and Psychotherapy, University of Gottingen, 37073 Gottingen, Germany
- 189 Psychiatry and Psychotherapy Clinic, University of Erlangen, 91054 Erlangen, Germany
- 190 Hunter New England Health Service, Newcastle NSW 2308, Australia
- 191 Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland 20892, USA
- 192 Research and Development, Bronx Veterans Affairs Medical Center, New York, New York 10468, USA
- 193 Wellcome Trust Centre for Human Genetics, Oxford, OX3 7BN, UK
- 194 Department of Clinical Neurology, Medical University of Vienna, 1090 Wien, Austria
- 195 Lieber Institute for Brain Development, Baltimore, Maryland 21205, USA
- 196 Department of Medical Genetics, University Medical Centre Utrecht, Universiteitsweg 100, 3584 CG, Utrecht, The Netherlands
- 197 Berkshire Healthcare NHS Foundation Trust, Bracknell RG12 1BQ, UK
- 198 Department of Medical Genetics, Medical University, Sofia 1431, Bulgaria
- 199 Priority Research Centre for Translational Neuroscience and Mental Health, University of Newcastle, Newcastle NSW 2300, Australia
- 200 Department of Psychiatry, University of Oulu, PO BOX 5000, 90014, Finland
- 201 University Hospital of Oulu, PO BOX 20, 90029 OYS, Finland
- 202 Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin 2, Ireland
- 203 Health Research Board, Dublin 2, Ireland
- 204 Mental Health Centre and Psychiatric Laboratory, West China Hospital, Sichuan University, Chendu, 610041, Sichuan, China
- 205 School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Perth WA 6009, Australia



- 206 Computational Sciences CoE, Pfizer Worldwide Research and Development, Cambridge, Massachusetts 02139, USA
- 207 Human Genetics, Genome Institute of Singapore, A\*STAR, Singapore 138672, Singapore
- 208 WTCCC2
- 209 Division of Psychiatry, University of Edinburgh, Edinburgh EH16 4SB, UK
- 210 University College London, London WC1E 6BT, UK 211 Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA
- 212 Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, 52428 Juelich, Germany
- 213 Department of Genetics, The Hebrew University of Jerusalem, 91905 Jerusalem, Israel
- 214 Neuroscience Discovery and Translational Area, Pharma Research and Early Development, F.Hoffman-La Roche, CH-4070 Basel, Switzerland
- 215 School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Perth, WA 6009, Australia
- 216 Centre for Clinical Research in Neuropsychiatry, School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Medical Research Foundation Building, Perth WA 6000, Australia
- 217 The Perkins Institute for Medical Research, The University of Western Australia, Perth, WA 6009, Australia
- 218 The Zucker Hillside Hospital, Glen Oaks, New York 11004, USA
- 219 The Feinstein Institute for Medical Research, Manhasset, New York 11030, USA
- 220 The Hofstra NS-LIJ School of Medicine, Hempstead, New York 11549, USA
- 221 Saw Swee Hock School of Public Health, National University of Singapore, Singapore 117597, Singapore
- 222 Queensland Brain Institute, The University of Queensland, Brisbane QLD 4072, Australia
- 223 Department of Functional Genomics, Center for Neurogenomics and Cognitive Research, Neuroscience Campus Amsterdam, VU University, Amsterdam 1081, The Netherlands
- 224 Department of Complex Trait Genetics, Neuroscience Campus Amsterdam, VU University Medical Center Amsterdam, Amsterdam 1081, The Netherlands

225 Department of Child and Adolescent Psychiatry, Erasmus University Medical Centre, Rotterdam 3000, The Netherlands

226 University of Aberdeen, Institute of Medical Sciences, Aberdeen, AB25 2ZD, UK

227 Departments of Psychiatry, Neurology, Neuroscience and Institute of Genetic Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland 21205, USA

## ENIGMA2 consortium collaborators include

Derrek P Hibar<sup>5</sup>, Jason L Stein<sup>1,5,6</sup>, Miguel E Renteria<sup>35</sup>, Alejandro Arias-Vasquez<sup>2,3,4,10</sup>, Sylvane Desrivieres<sup>228</sup>, Neda Jahanshad<sup>229</sup>, Roberto Toro<sup>230</sup>, Katharina Wittfeld<sup>231,232</sup>, Lucija Abramovic<sup>233</sup>, Micael Andersson<sup>234</sup>, Benjamin S Aribisala<sup>235,236,237</sup>, Nicola J Armstrong<sup>25</sup>, Manon Bernard<sup>238</sup>, Marc M Bohlken<sup>233</sup>, Marco P Boks<sup>233</sup>, Janita Bralten<sup>2,4,10</sup>, Andrew A Brown<sup>22</sup>, M Mallar Chakravarty<sup>239,240</sup>, Qiang Chen<sup>195</sup>, Christopher R K Ching<sup>229</sup>, Gabriel Cuellar-Partida<sup>35</sup>, Anouk den Braber<sup>241</sup>, Sudheer Giddaluru<sup>242,243</sup>, Aaron L Goldman<sup>195</sup>, Oliver Grimm<sup>18</sup>, Tulio Guadalupe<sup>244,245</sup>, Johanna Hass<sup>32</sup>, Girma Woldehawariat<sup>246</sup>, Avram J Holmes<sup>63</sup>, Martine Hoogman<sup>2,4</sup>, Deborah Janowitz<sup>232</sup>, Tianye Jia<sup>228</sup>, Sungeun Kim<sup>29,30</sup>, Marieke Klein<sup>2,4</sup>, Bernd Kraemer<sup>24</sup>, Phil Lee<sup>8,11,12</sup>, Loes M Olde Loohuis<sup>247</sup>, Michelle Luciano<sup>248</sup>, Christine Macare<sup>228</sup>, Karen A Mather<sup>25</sup>, Manuel Mattheisen<sup>19,20,21</sup>, Yuri Milaneschi<sup>249</sup>, Kwangsik Nho<sup>29,30</sup>, Martina Pappmeyer<sup>16</sup>, Adaikalavan Ramasamy<sup>250,251</sup>, Shannon L Risacher<sup>29,30</sup>, Roberto Roiz-Santiañez<sup>27,28</sup>, Emma J Rose<sup>45</sup>, Alireza Salami<sup>234</sup>, Philipp G Sämann<sup>252</sup>, Lianne Schmaal<sup>249</sup>, Andrew J Schork<sup>253,254</sup>, Jean Shin<sup>238</sup>, Lachlan T Strike<sup>35,36</sup>, Alexander Teumer<sup>255</sup>, Marjolein M J van Donkelaar<sup>2,4</sup>, Kristel R van Eijk<sup>233</sup>, Raymond K Walters<sup>7,41</sup>, Lars T Westlye<sup>256,257</sup>, Christopher D Whelan<sup>258</sup>, Anderson M Winkler<sup>259</sup>, Marcel P Zwiers<sup>4</sup>, Saud Alhusaini<sup>258,260</sup>, Lavinia Athanasia<sup>22</sup>, Stefan Ehrlich<sup>32</sup>, Marina M H Hakobjan<sup>2,4</sup>, Cecilie B Hartberg<sup>22</sup>, Unn Haukvik<sup>22</sup>, Angelien J G A M Heister<sup>2,4</sup>, David Höhn<sup>252</sup>, Dalia Kasperaviciute<sup>261,262</sup>, David C M Liewald<sup>248</sup>, Lorna M Lopez<sup>248</sup>, Remco R R Makkinje<sup>2,4</sup>, Mar Matarin<sup>261</sup>, Marlies A M Naber<sup>2,4</sup>, David R McKay<sup>263,264</sup>, Margaret Needham<sup>45</sup>, Allison C Nugent<sup>246</sup>, Benno Pütz<sup>252</sup>, Natalie A Royle<sup>235,237,248</sup>, Li Shen<sup>29,30</sup>, Emma Sprooten<sup>16</sup>, Daniah Trabzuni<sup>251,265</sup>, Saskia S L van der Marel<sup>2,4</sup>, Kimm J E van Hulzen<sup>2,4</sup>, Esther Walton<sup>32</sup>, Christiane Wolf<sup>252</sup>, Laura Almasy<sup>266</sup>, David Ames<sup>267,268</sup>, Sampath Arepalli<sup>269</sup>, Amelia A Assareh<sup>25</sup>, Mark E Bastin<sup>235,237,248,270</sup>, Henry Brodaty<sup>25</sup>, Kazima B Bulayeva<sup>271</sup>, Melanie A Carless<sup>266</sup>, Sven Cichon<sup>90,91,125,212</sup>, Aiden Corvin<sup>45</sup>, Joanne E Curran<sup>266</sup>, Michael Czisch<sup>252</sup>, Greig I de Zubicaray<sup>36</sup>, Allissa Dillman<sup>269</sup>, Ravi Duggirala<sup>266</sup>, Thomas D Dyer<sup>266</sup>, Susanne Erk<sup>9</sup>, Iryna O Fedko<sup>241</sup>, Luigi Ferrucci<sup>272</sup>, Tatiana M Foroud<sup>30,31</sup>, Peter T Fox<sup>273</sup>, Masaki Fukunaga<sup>274</sup>, Raphael Gibbs<sup>251,269</sup>, Harald H H Göring<sup>266</sup>, Robert C Green<sup>275,276</sup>, Sebastian Guelfi<sup>251</sup>, Narelle K Hansell<sup>35</sup>, Catharina A Hartman<sup>277</sup>, Katrin Hegenscheid<sup>278</sup>, Andreas Heinz<sup>9</sup>, Dena G Hernandez<sup>251,269</sup>, Dirk J Heslenfeld<sup>279</sup>, Pieter J Hoekstra<sup>277</sup>, Florian Holsboer<sup>252</sup>, Georg Homuth<sup>280</sup>, Jouke-Jan Hottenga<sup>241</sup>, Masashi Ikeda<sup>127</sup>, Clifford R Jack Jr<sup>281</sup>, Mark Jenkinson<sup>282</sup>, Robert Johnson<sup>283</sup>, Ryota Kanai<sup>284,285</sup>, Maria Keil<sup>24</sup>, Jack W Kent Jr<sup>266</sup>, Peter Kochunov<sup>286</sup>, John B Kwok<sup>287,288</sup>, Stephen M Lawrie<sup>16</sup>, Xinmin Liu<sup>246,289</sup>, Dan L Longo<sup>290</sup>, Katie L McMahon<sup>291</sup>, Eva Meisenzahl<sup>292</sup>, Ingrid Melle<sup>23</sup>, Sebastian Mohnke<sup>9</sup>, Grant W Montgomery<sup>35</sup>, Jeanette C Mostert<sup>2,4</sup>, Thomas W Mühleisen<sup>212</sup>, Michael A

Nalls <sup>269</sup>, Thomas E Nichols <sup>13,14</sup>, Lars G Nilsson <sup>234</sup>, Markus M Nöthen <sup>90,91</sup>, Kazutaka Ohi <sup>293</sup>, Rene L Olvera <sup>273</sup>, Rocio Perez-Iglesias <sup>28,177</sup>, G Bruce Pike <sup>294,295</sup>, Steven G Potkin <sup>296</sup>, Ivar Reinvang <sup>257</sup>, Simone Reppermund <sup>25</sup>, Marcella Rietschel <sup>109</sup>, Nina Romanczuk-Seifert <sup>9</sup>, Glenn D Rosen <sup>297,298</sup>, Dan Rujescu <sup>114,115</sup>, Knut Schnell <sup>188</sup>, Peter R Schofield <sup>287,288</sup>, Colin Smith <sup>299</sup>, Vidar M Steen <sup>242,243</sup>, Jessika E Sussmann <sup>16</sup>, Anbupalam Thalamuthu <sup>25</sup>, Arthur W Toga <sup>300</sup>, Bryan Traynor <sup>269</sup>, Juan Troncoso <sup>301</sup>, Jessica A Turner <sup>33,34</sup>, Maria C Valdés Hernández <sup>270</sup>, Dennis van 't Ent <sup>241</sup>, Marcel van der Brug <sup>302</sup>, Nic J A van der Wee <sup>303</sup>, Marie-Jose van Tol <sup>304</sup>, Dick J Veltman <sup>249</sup>, Thomas H Wassink <sup>305</sup>, Eric Westman <sup>306</sup>, Ronald H Zielke <sup>283</sup>, Alan Zonderman <sup>307</sup>, David G Ashbrook <sup>308</sup>, Reinmar Hager <sup>308</sup>, Lu Lu <sup>309,310</sup>, Francis J McMahon <sup>17</sup>, Derek W Morris <sup>45,96</sup>, Robert W Williams <sup>309,310</sup>, Han G Brunner <sup>2,4</sup>, Randy L Buckner <sup>62,63,64</sup>, Jan K Buitelaar <sup>4,10</sup>, Wiepke Cahn <sup>66</sup>, Vince D Calhoun <sup>311,312</sup>, Gianpiero L Cavalleri <sup>258</sup>, Benedicto Crespo-Facorro <sup>85,86</sup>, Anders M Dale <sup>313,314</sup>, Gareth E Davies <sup>315</sup>, Norman Delanty <sup>258,316</sup>, Chantal Depondt <sup>317</sup>, Srdjan Djurovic <sup>48,95</sup>, Wayne C Drevets <sup>246,318</sup>, Thomas Espeseth <sup>256,257</sup>, Randy L Gollub <sup>63</sup>, Beng-Choon Ho <sup>319</sup>, Wolfgang Hoffmann <sup>231,255</sup>, Norbert Hosten <sup>278</sup>, René S Kahn <sup>66</sup>, Stephanie Le Hellard <sup>242,243</sup>, Andreas Meyer-Lindenberg <sup>18</sup>, Bertram Müller-Myhsok <sup>162,163,164</sup>, Matthias Nauck <sup>320</sup>, Lars Nyberg <sup>234</sup>, Massimo Pandolfo <sup>317</sup>, Brenda W J H Penninx <sup>249</sup>, Joshua L Roffman <sup>63,64</sup>, Sanjay M Sisodiya <sup>261</sup>, Jordan W Smoller <sup>8,11,12</sup>, Hans van Bokhoven <sup>2,4</sup>, Neeltje E M van Haren <sup>233</sup>, Henry Völzke <sup>255</sup>, Henrik Walter <sup>9</sup>, Michael W Weiner <sup>321</sup>, Wei Wen <sup>25</sup>, Tonya White <sup>322,323</sup>, Ingrid Agartz <sup>48,49,50</sup>, Ole A Andreassen <sup>22,23</sup>, John Blangero <sup>266</sup>, Dorret I Boomsma <sup>241</sup>, Rachel M Brouwer <sup>233</sup>, Dara M Cannon <sup>246,324</sup>, Mark R Cookson <sup>269</sup>, Eco J C de Geus <sup>241</sup>, Ian J Deary <sup>248</sup>, Gary Donohoe <sup>45,96</sup>, Guillén Fernández <sup>4,10</sup>, Simon E Fisher <sup>4</sup>, Clyde Francks <sup>4</sup>, David C Glahn <sup>263,264</sup>, Hans J Grabe <sup>232,325</sup>, Oliver Gruber <sup>24</sup>, John Hardy <sup>251</sup>, Ryota Hashimoto <sup>326</sup>, Hilleke E Hulshoff Pol <sup>233</sup>, Erik G Jönsson <sup>48,50</sup>, Iwona Kloszewska <sup>327</sup>, Simon Lovestone <sup>184</sup>, Venkata S Mattay <sup>195</sup>, Patrizia Mecocci <sup>328</sup>, Colm McDonald <sup>156</sup>, Andrew M McIntosh <sup>16</sup>, Roel A Ophoff <sup>66,73,112</sup>, Tomas Paus <sup>329,330</sup>, Zdenka Pausova <sup>238,331</sup>, Mina Ryten <sup>250,251</sup>, Perminder S Sachdev <sup>25,26</sup>, Andrew J Saykin <sup>29,30,31</sup>, Andy Simmons <sup>332,333,334</sup>, Andrew Singleton <sup>269</sup>, Hilka Soininen <sup>335,336</sup>, Joanna M Wardlaw <sup>235,237,248,270</sup>, Michael E Weale <sup>250</sup>, Daniel R Weinberger <sup>195,227</sup>, Hieab H H Adams <sup>323,337</sup>, Lenore J Launer <sup>338</sup>, Stephan Seiler <sup>339</sup>, Reinhold Schmidt <sup>339</sup>, Ganesh Chauhan <sup>340</sup>, Claudia L Satizabal <sup>341,342</sup>, James T Becker <sup>343,344,345</sup>, Lisa Yanek <sup>346</sup>, Sven J van der Lee <sup>337</sup>, Maritza Ebling <sup>347,348</sup>, Bruce Fischl <sup>347,348</sup>, W T Longstreth <sup>349</sup>, Douglas Greve <sup>347,348</sup>, Helena Schmidt <sup>350</sup>, Paul Nyquist <sup>351</sup>, Louis N Vinke <sup>347,348</sup>, Cornelia M van Duijn <sup>337</sup>, Xue Luting <sup>352</sup>, Bernard Mazoyer <sup>353</sup>, Joshua C Bis <sup>354</sup>, Vilmundur Gudnason <sup>355</sup>, Sudha Seshadri <sup>341,342</sup>, M Arfan Ikram <sup>323,337</sup>, Nicholas G Martin <sup>35</sup>, Margaret J Wright <sup>35,36</sup>, Gunter Schumann <sup>228</sup>, Barbara Franke <sup>1,2,3,4</sup>, Paul M Thompson <sup>5,38</sup>, Sarah E Medland <sup>35,38</sup>

228 MRC-SGDP Centre, Institute of Psychiatry, King's College London, London, SE5 8AF, UK

229 Imaging Genetics Center, Institute for Neuroimaging & Informatics, Keck School of Medicine of the University of Southern California, Los Angeles, 90292, USA

230 Institut Pasteur, Paris, 75015, France

- 231 German Center for Neurodegenerative Diseases (DZNE) Rostock/Greifswald, Greifswald, 17487, Germany
- 232 Department of Psychiatry, University Medicine Greifswald, Greifswald, 17489, Germany
- 233 Brain Center Rudolf Magnus, Department of Psychiatry, UMC Utrecht, Utrecht, 3584, The Netherlands
- 234 Umeå Centre for Functional Brain Imaging (UFBI), Umeå University, Umeå, 901 87, Sweden
- 235 Brain Research Imaging Centre, University of Edinburgh, Edinburgh, EH4 2XU, UK
- 236 Department of Computer Science, Lagos State University, Lagos, Nigeria
- 237 Scottish Imaging Network, A Platform for Scientific Excellence (SINAPSE) Collaboration, Department of Neuroimaging Sciences, University of Edinburgh, Edinburgh, EH4 2XU, UK
- 238 Hospital for Sick Children, University of Toronto, Toronto, M5G 1X8, Canada
- 239 Cerebral Imaging Centre, Douglas Mental Health University Institute, Montreal, H4H 1R3, Canada
- 240 Department of Psychiatry and Biomedical Engineering, McGill University, Montreal, H3A 2B4, Canada
- 241 Biological Psychology, Neuroscience Campus Amsterdam, VU University & VU Medical Center, Amsterdam, 1081 BT, The Netherlands
- 242 NORMENT - KG Jebsen Centre for Psychosis Research, Department of Clinical Science, University of Bergen, 5021, Norway
- 243 Dr Einar Martens Research Group for Biological Psychiatry, Center for Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, 5021, Norway
- 244 Language and Genetics Department, Max Planck Institute for Psycholinguistics, Nijmegen, 6525 XD, The Netherlands
- 245 International Max Planck Research School for Language Sciences, Nijmegen, 6525 XD, The Netherlands
- 246 National Institute of Mental Health Intramural Research Program, Bethesda, 20892, USA
- 247 Center for Neurobehavioral Genetics, University of California, Los Angeles, California, 90095, USA

- 248 Centre for Cognitive Ageing and Cognitive Epidemiology, Psychology, University of Edinburgh, Edinburgh, EH8 9JZ, UK
- 249 Department of Psychiatry, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, 1007 MB, The Netherlands
- 250 Department of Medical and Molecular Genetics, King's College London, London, SE1 9RT, UK
- 251 Reta Lila Weston Institute and Department of Molecular Neuroscience, UCL Institute of Neurology, London, WC1N 3BG, UK
- 252 Max Planck Institute of Psychiatry, Munich, 80804, Germany
- 253 Multimodal Imaging Laboratory, Department of Neurosciences, University of California, San Diego, 92093, USA
- 254 Department of Cognitive Sciences, University of California, San Diego, 92161, USA
- 255 Institute for Community Medicine, University Medicine Greifswald, Greifswald, 17489, Germany
- 256 NORMENT - KG Jebsen Centre, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, 0315, Norway
- 257 NORMENT - KG Jebsen Centre, Department of Psychology, University of Oslo, Oslo, 0373, Norway
- 258 Molecular and Cellular Therapeutics, The Royal College of Surgeons, Dublin, 2, Ireland
- 259 The Oxford Center for Functional MRI of the Brain, Nuffield Department of Clinical Neurosciences, Oxford University, Oxford, OX3 9DU, UK
- 260 Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, H3A 2B4, Canada
- 261 UCL Institute of Neurology, London, United Kingdom and Epilepsy Society, WC1N 3BG, UK
- 262 Department of Medicine, Imperial College London, London, SW7 2AZ, UK
- 263 Department of Psychiatry, Yale University, New Haven, Connecticut, 06511, USA
- 264 Olin Neuropsychiatric Research Center, Hartford, Connecticut, 06114, USA
- 265 Department of Genetics, King Faisal Specialist Hospital and Research Centre, Riyadh, 12713, Saudi Arabia
- 266 Texas Biomedical Research Institute, San Antonio, Texas, 78227, USA

- 267 National Ageing Research Institute, Royal Melbourne Hospital, Melbourne, 3052, Australia
- 268 Academic Unit for Psychiatry of Old Age, University of Melbourne, 3101, Australia
- 269 Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, 20892, USA
- 270 Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, EH4 2XU, UK
- 271 NI Vavilov Institute of General Genetics, Russian Academy of Sciences, Moscow, 119333, Russia
- 272 Clinical Research Branch, National Institute on Aging, Baltimore, Maryland, 20892, USA
- 273 University of Texas Health Science Center, San Antonio, 78229, USA
- 274 Biofunctional Imaging, Immunology Frontier Research Center, Osaka University, Osaka, 565-0871, Japan
- 275 Harvard Medical School, Cambridge, Massachusetts, 02115, USA
- 276 Division of Genetics, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, 02115, USA
- 277 Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, 9700, The Netherlands
- 278 Institute of Diagnostic Radiology and Neuroradiology, University Medicine Greifswald, Greifswald, 17489, Germany
- 279 Department of Psychology, VU University Amsterdam, Amsterdam, 1081 BT, The Netherlands
- 280 Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald, 17489, Germany
- 281 Radiology, Mayo Clinic, Rochester, Minnesota, 55905, USA
- 282 FMRIB Centre, University of Oxford, Oxford, OX3 9DU, UK
- 283 NICHD Brain and Tissue Bank for Developmental Disorders, University of Maryland Medical School, Baltimore, Maryland, 21201, USA
- 284 School of Psychology, University of Sussex, Brighton, BN1 9QH, UK
- 285 Institute of Cognitive Neuroscience, University College London, London, WC1N 3AR, UK



- 286 Department of Psychiatry, University of Maryland, Catonsville, Maryland, 21201, USA
- 287 Neuroscience Research Australia, Sydney, 2031, Australia
- 288 School of Medical Sciences, UNSW, Sydney, 2052, Australia
- 289 Columbia University Medical Center, New York, 10032, USA
- 290 Lymphocyte Cell Biology Unit, Laboratory of Immunology, National Institute on Aging, National Institutes of Health, Baltimore, Maryland, 21224, USA
- 291 Centre for Advanced Imaging, University of Queensland, Brisbane, 4072, Australia
- 292 Ludwig-Maximilians-Universität, Munich, 80539, Germany
- 293 Department of Psychiatry, Osaka University Graduate School of Medicine, Osaka, 565-0871, Japan
- 294 Department of Neurology, University of Calgary, Calgary, T2N 2T9, Canada
- 295 Department of Clinical Neuroscience, University of Calgary, Calgary, T2N 2T9, Canada
- 296 Psychiatry and Human Behavior, University of California, Irvine, California, 92697, USA
- 297 Beth Israel Deaconess Medical Center, Boston, Massachusetts, 02215, USA
- 298 Department of Neurology, Harvard Medical School, Boston, Massachusetts, 02115, USA
- 299 Department of Neuropathology, MRC Sudden Death Brain Bank Project, University of Edinburgh, Edinburgh, EH8 9AG, UK
- 300 Laboratory of Neuro Imaging, Institute for Neuroimaging and Informatics, Keck School of Medicine of the University of Southern California, Los Angeles, California, 90033, USA
- 301 Brain Resource Center, Johns Hopkins University, Baltimore, Maryland, 21287, USA
- 302 The Scripps Research Institute, Jupiter, Florida, 33458, USA
- 303 Leiden University Medical Center, Leiden, 2333 ZA, The Netherlands
- 304 Neuroimaging Centre, University of Groningen, University Medical Center Groningen, Groningen, 9713 AW, The Netherlands
- 305 Department of Psychiatry, Carver College of Medicine, University of Iowa, Iowa City, 52242, USA
- 306 Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, SE-141 83, Sweden

307 Research Resources Branch, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, 20892, USA

308 Faculty of Life Sciences, University of Manchester, Manchester, M13 9PL, UK

309 Center for Integrative and Translational Genomics, University of Tennessee Health Science Center, Memphis, Tennessee, 38163, USA

310 Department of Anatomy and Neurobiology, University of Tennessee Health Science Center, Memphis, Tennessee, 38163, USA

311 The Mind Research Network & LBERI, Albuquerque, New Mexico, 87106, USA

312 Department of ECE, University of New Mexico, Albuquerque, New Mexico, 87131, USA

313 Center for Translational Imaging and Personalized Medicine, University of California, San Diego, 92093, California, USA

314 Departments of Neurosciences, Radiology, Psychiatry, and Cognitive Science, University of California, San Diego, 92093, California, USA

315 Avera Institute for Human Genetics, Sioux Falls, 57108, USA

316 Neurology Division, Beaumont Hospital, Dublin, 9, Ireland

317 Department of Neurology, Hopital Erasme, Universite Libre de Bruxelles, Brussels, 1070, Belgium

318 Janssen Research & Development, Johnson & Johnson, New Jersey, 08560, USA

319 Department of Psychiatry, University of Iowa, Iowa City, 52242, USA

320 Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, 17489, Germany

321 Center for Imaging of Neurodegenerative Disease, San Francisco VA Medical Center, University of California, San Francisco, 94121, USA

322 Department of Child Psychiatry, Erasmus University Medical Centre, Rotterdam, 3015 CE, The Netherlands

323 Department of Radiology, Erasmus University Medical Centre, Rotterdam, 3015 CE, The Netherlands

324 Clinical Neuroimaging Laboratory, College of Medicine, Nursing and Health Sciences, National University of Ireland Galway, Galway, SW4 794, Ireland

325 Department of Psychiatry and Psychotherapy, HELIOS Hospital Stralsund, 18435, Germany

- 326 Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Osaka, 565-0871, Japan
- 327 Medical University of Lodz, Lodz, 90-419, Poland
- 328 Section of Gerontology and Geriatrics, Department of Medicine, University of Perugia, Perugia, 06123, Italy
- 329 Rotman Research Institute, University of Toronto, Toronto, M6A 2E1, Canada
- 330 Departments of Psychology and Psychiatry, University of Toronto, M5T 1R8, Canada
- 331 Departments of Physiology and Nutritional Sciences, University of Toronto, M5S 3E2, Canada
- 332 Department of Neuroimaging, Institute of Psychiatry, King's College London, London, SE5 8AF, UK
- 333 Biomedical Research Centre for Mental Health, King's College London, London, SE5 8AF, UK
- 334 Biomedical Research Unit for Dementia, King's College London, London, SE5 8AF, UK
- 335 Institute of Clinical Medicine, Neurology, University of Eastern Finland, Kuopio, FI-70211, Finland
- 336 Neurocentre Neurology, Kuopio University Hospital, FI-70211, Finland
- 337 Department of Epidemiology, Erasmus University Medical Centre, Rotterdam, 3015 GE, The Netherlands
- 338 Laboratory of Epidemiology and Population Sciences, Intramural Research Program, National Institute on Aging, Bethesda, Maryland, 20892, USA
- 339 Department of Neurology, Clinical Division of Neurogeriatrics, Medical University Graz, Graz, 8036, Austria
- 340 INSERM U897, University of Bordeaux, 33076, France
- 341 Department of Neurology, Boston University School of Medicine, Boston, Massachusetts, 02118, USA
- 342 Framingham Heart Study, Framingham, 01702, USA
- 343 Department of Neurology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, 15213, USA
- 344 Department of Psychiatry, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, 15213, USA

345 Department of Psychology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, 15213, USA

346 General Internal Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, 21205, USA

347 Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, 02129, USA

348 Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, 02114, USA

349 Department of Neurology University of Washington, Seattle, 98104, USA

350 Institute of Molecular Biology and Biochemistry, Medical University Graz, 8036, Austria

351 Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, 21205, USA

352 Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, 02118, USA

353 UMR5296 CNRS, CEA and University of Bordeaux, Bordeaux, 33076, France

354 Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, 98101, USA

355 Icelandic Heart Association, Kopavogur, University of Iceland, Faculty of Medicine, Reykjavik, 101, Iceland

## References

1. Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nature Reviews Genetics*. 2012; 13:537–51.
2. Purcell SM, et al. A polygenic burden of rare disruptive mutations in schizophrenia. *Nature*. 2014; 506:185–90. [PubMed: 24463508]
3. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014; 511:421–7. [PubMed: 25056061]
4. Network & Pathway Analysis Subgroup of Psychiatric Genomics, C. Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. *Nat Neurosci*. 2015; 18:199–209. [PubMed: 25599223]
5. van Erp TG, et al. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Mol Psychiatry*. 2015
6. Haijma SV, et al. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. *Schizophr Bull*. 2013; 39:1129–38. [PubMed: 23042112]
7. Boos HB, Aleman A, Cahn W, Hulshoff Pol H, Kahn RS. Brain volumes in relatives of patients with schizophrenia: a meta-analysis. *Arch Gen Psychiatry*. 2007; 64:297–304. [PubMed: 17339518]
8. Thermenos HW, et al. A review of neuroimaging studies of young relatives of individuals with schizophrenia: a developmental perspective from schizotaxia to schizophrenia. *Am J Med Genet B Neuropsychiatr Genet*. 2013; 162B:604–35. [PubMed: 24132894]

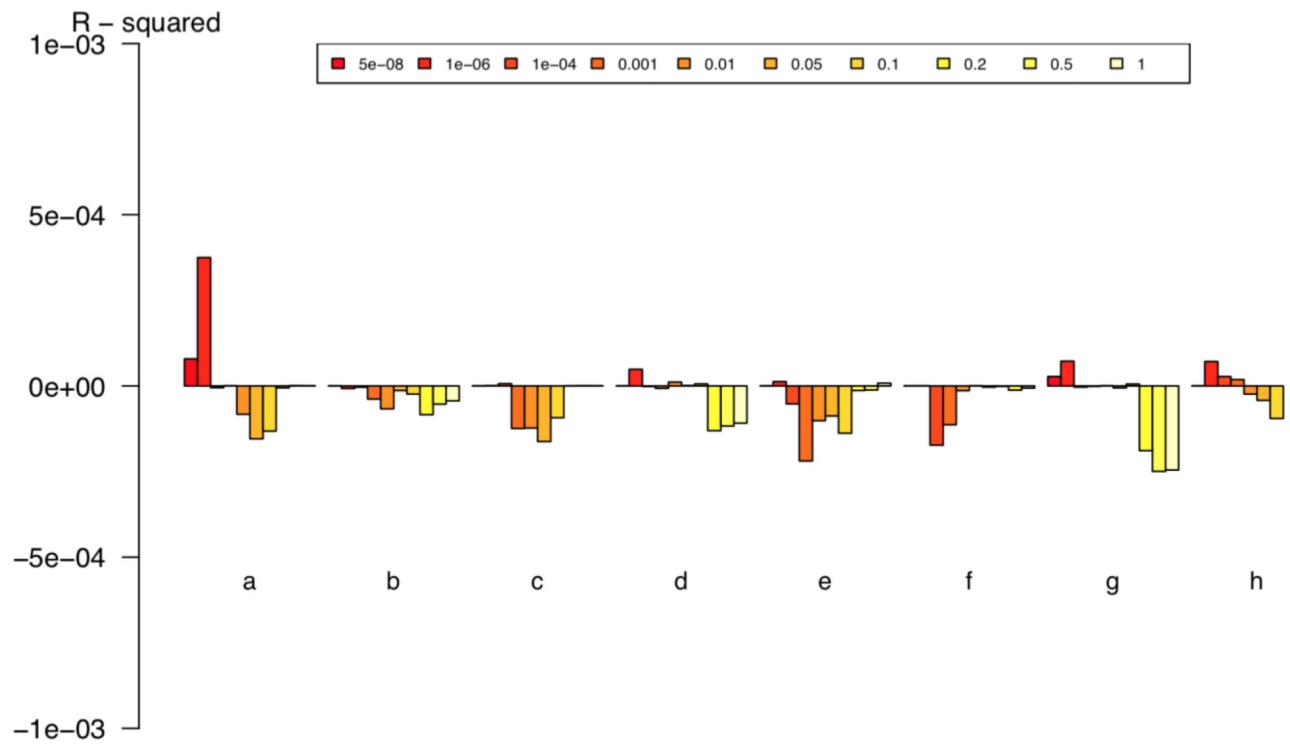
9. Hibar DP, et al. Common genetic variants influence human subcortical brain structures. *Nature*. 2015
10. Blokland GA, de Zubicaray GI, McMahon KL, Wright MJ. Genetic and environmental influences on neuroimaging phenotypes: a meta-analytical perspective on twin imaging studies. *Twin Res Hum Genet*. 2012; 15:351–71. [PubMed: 22856370]
11. Stefansson H, et al. CNVs conferring risk of autism or schizophrenia affect cognition in controls. *Nature*. 2014; 505:361–6. [PubMed: 24352232]
12. Bulik-Sullivan BK, et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nature Genetics*. 2015; 47:291–5. [PubMed: 25642630]
13. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature genetics*. 2013; 45:984–94. [PubMed: 23933821]
14. Bulik-Sullivan BK, et al. An atlas of genetic correlations across human diseases and traits. *Nature Genetics*. 2015
15. International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. 2009; 460:748–52. [PubMed: 19571811]
16. Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet*. 2013; 381:1371–9. [PubMed: 23453885]
17. Plaisier SB, Taschereau R, Wong JA, Graeber TG. Rank-rank hypergeometric overlap: identification of statistically significant overlap between gene-expression signatures. *Nucleic Acids Res*. 2010; 38:e169. [PubMed: 20660011]
18. Ho YYW. Variants within ADAMTS9-AS2 influence whorls in fingerprint patterns. Submitted.
19. Nichols T, Brett M, Andersson J, Wager T, Poline JB. Valid conjunction inference with the minimum statistic. *Neuroimage*. 2005; 25:653–60. [PubMed: 15808966]
20. Rose EJ, Donohoe G. Brain vs behavior: an effect size comparison of neuroimaging and cognitive studies of genetic risk for schizophrenia. *Schizophr Bull*. 2013; 39:518–26. [PubMed: 22499782]
21. Mier D, Kirsch P, Meyer-Lindenberg A. Neural substrates of pleiotropic action of genetic variation in COMT: a meta-analysis. *Mol Psychiatry*. 2010; 15:918–27. [PubMed: 19417742]
22. Hariri AR, Weinberger DR. Imaging genomics. *Br Med Bull*. 2003; 65:259–70. [PubMed: 12697630]
23. Witte JS, Visscher PM, Wray NR. The contribution of genetic variants to disease depends on the ruler. *Nat Rev Genet*. 2014; 15:765–76. [PubMed: 25223781]
24. Wood AR, et al. Defining the role of common variation in the genomic and biological architecture of adult human height. *Nat Genet*. 2014; 46:1173–86. [PubMed: 25282103]
25. Touloupoulou T, et al. Reciprocal causation models of cognitive vs volumetric cerebral intermediate phenotypes for schizophrenia in a pan-European twin cohort. *Mol Psychiatry*. 2014
26. Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch Gen Psychiatry*. 2009; 66:811–22. [PubMed: 19652121]
27. Narr KL, et al. Mapping cortical thickness and gray matter concentration in first episode schizophrenia. *Cereb Cortex*. 2005; 15:708–19. [PubMed: 15371291]
28. Weinberger DR. On the plausibility of “the neurodevelopmental hypothesis” of schizophrenia. *Neuropsychopharmacology*. 1996; 14:1S–11S. [PubMed: 8866738]
29. Visscher PM, Brown MA, McCarthy MI, Yang J. Five Years of GWAS Discovery. *American journal of human genetics*. 2012; 90:7–24. [PubMed: 22243964]
30. Ge T, et al. Massively expedited genome-wide heritability analysis (MEGHA). *Proc Natl Acad Sci U S A*. 2015; 112:2479–84. [PubMed: 25675487]
31. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003; 160:636–45. [PubMed: 12668349]
32. Kendler KS, Neale MC. Endophenotype: a conceptual analysis. *Mol Psychiatry*. 2010; 15:789–97. [PubMed: 20142819]

33. Cannon TD, Keller MC. Endophenotypes in the genetic analyses of mental disorders. *Annual Review of Clinical Psychology*. 2006; 2:267–90.
34. Fuchsberger C, Abecasis GR, Hinds DA. minimac2: faster genotype imputation. *Bioinformatics*. 2015; 31:782–4. [PubMed: 25338720]
35. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics*. 2010; 26:2190–1. [PubMed: 20616382]
36. Deng X, Xu J, Wang C. Improving the power for detecting overlapping genes from multiple DNA microarray-derived gene lists. *BMC Bioinformatics*. 2008; 9(Suppl 6):S14. [PubMed: 18541049]
37. Storey JD. A direct approach to false discovery rates. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*. 2002; 63:479–98.
38. Rietveld CA, et al. GWAS of 126,559 individuals identifies genetic variants associated with educational attainment. *Science*. 2013; 340:1467–71. [PubMed: 23722424]

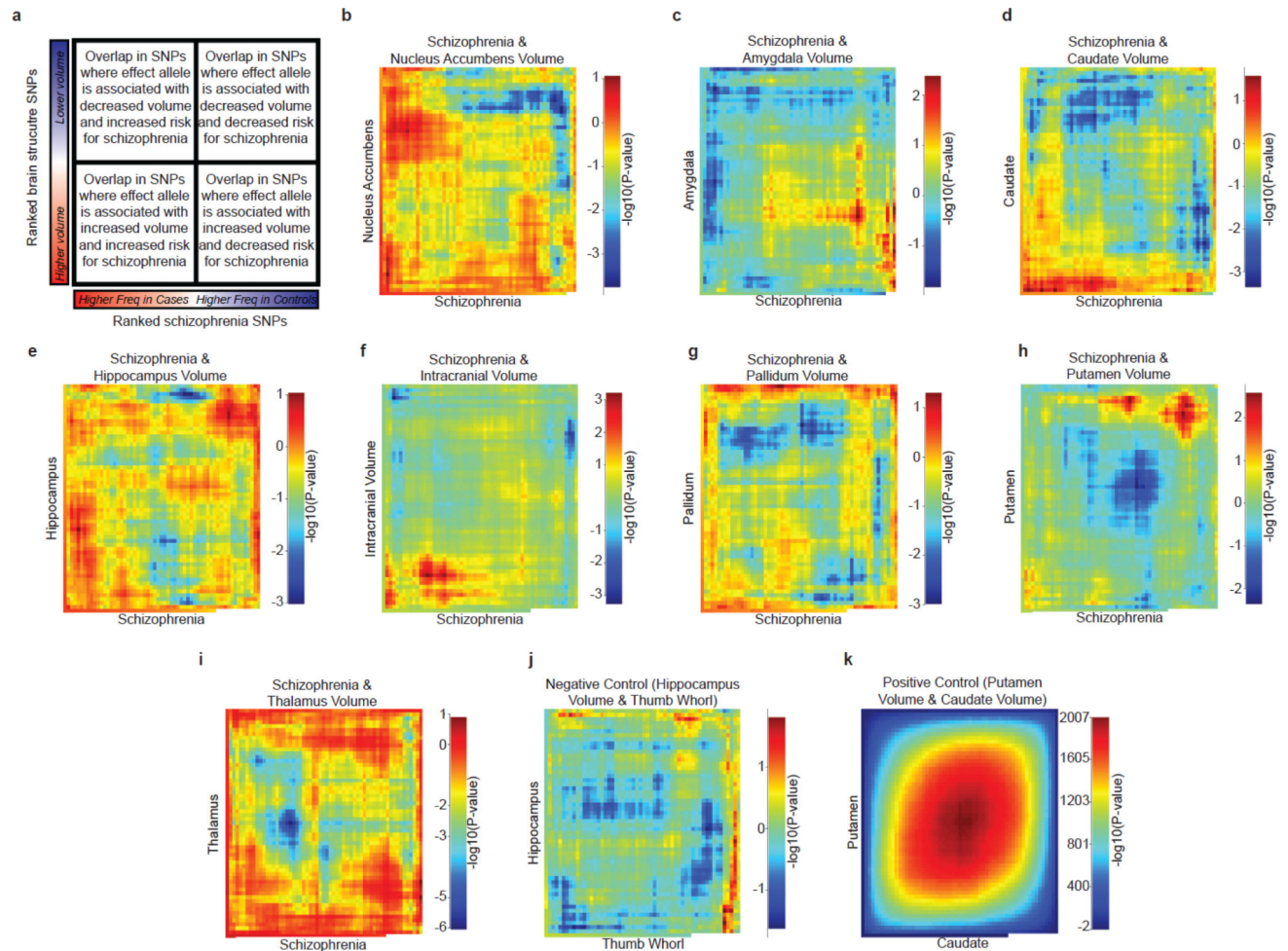


### Summary

The authors defined a roadmap for the investigation of the genetic covariance between structural/functional brain phenotypes and risk for psychiatric disorders. Their proof-of-concept study using the largest available common variant datasets for schizophrenia and volumes of several (mainly subcortical) brain structures did not find evidence of genetic overlap.



**Figure 1.** Genetic predisposition score analyses examining the predictive capacity of ENIGMA brain volumetric results on schizophrenia case-control status using different  $P$ -value thresholds. X-axis: (a) hippocampus, (b) ICV, (c) nucleus accumbens, (d) amygdala, (e) caudate nucleus, (f) pallidum, (g) putamen, (h) thalamus. Y-axis shows Nagelkerke's  $R^2$ . Positive values indicate SNP effects for increasing brain structure volume and increased risk for schizophrenia. Negative values indicate SNP effects for decreasing brain structure volume in and increased risk for schizophrenia. Significance values are given in **Table 2**.



**Figure 2.**

Evaluating the genome-wide overlap between genetic influences on schizophrenia and subcortical volumes. (a) A cartoon describing the output map. (b-i) independent SNPs present in both ENIGMA and PGC schizophrenia results were selected independent of association to any phenotype (see on-line methods). Association results were ordered based on the significance of their association to the phenotype ( $-\log_{10}(P\text{-value})$  multiplied by the sign of the effect), and statistical significance was evaluated using RRHO test. The same test for overlap was conducted with a (j) finger whorl phenotype, expected to have no overlap with brain structure genetics, and (k) the overlap between caudate and putamen volume, expected to have very strong overlap. Overlap in the rank-ordered lists between genetic variants influencing any of the eight brain phenotypes and those creating risk for schizophrenia was not statistically significant. The overlap between hippocampal volume and presence of a whorl on the left thumb was used as a negative control and showed similar levels of overlap to brain structure and schizophrenia.

**Table 1**

SNP-heritability analyses for MRI brain volume and genetic correlations with schizophrenia<sup>\*</sup>.

<b>Brain region<sup>*</sup></b>	<b>N</b>	<b>Heritability</b>	<b>SE</b>	<b>Genetic correlation with SCZ</b>	<b>SE</b>	<b>Z</b>	<b>P</b>
Intracranial volume	9,826	0.157	0.050	−0.010	0.072	−0.137	0.891
Caudate nucleus	11,624	0.260	0.043	−0.095	0.057	−1.674	0.094
Hippocampus	11,621	0.135	0.041	−0.147	0.081	−1.826	0.068
Nucleus accumbens	11,603	0.105	0.045	−0.094	0.090	−1.051	0.293
Pallidum	11,595	0.137	0.047	−0.038	0.069	−0.546	0.585
Putamen	11,598	0.303	0.052	0.013	0.052	0.256	0.798
Thalamus	11,646	0.118	0.041	−0.113	0.087	−1.298	0.194

<sup>\*</sup> amygdala heritability was too low to allow a valid analysis

**Table 2**

Two outcome variables derived from genetic predisposition analysis.

Phenotype	P-	R <sup>2</sup>	AUC	OR (95% CI)
Intracranial volume	0.247	$-2.46 \times 10^{-5}$	0.512	0.944 (0.877,1.016)
Caudate nucleus	0.033	$-8.35 \times 10^{-5}$	0.502	0.928 (0.864,0.997)
Hippocampus	0.010	$-1.23 \times 10^{-4}$	0.506	0.917 (0.853,0.986)
Nucleus accumbens	0.002	$-1.74 \times 10^{-4}$	0.500	0.928 (0.862,0.9996)
Pallidum	0.985	$6.21 \times 10^{-9}$	0.513	1.034 (0.963,1.111)
Putamen	0.607	$-4.87 \times 10^{-6}$	0.515	0.971 (0.891,1.059)
Thalamus	0.221	$-2.75 \times 10^{-5}$	0.510	0.959 (0.888,1.036)
Amygdala	0.806	$1.11 \times 10^{-6}$	0.509	1.021 (0.951,1.096)

P=significance uncorrected for multiple testing. R<sup>2</sup>=correlation (Nagelkerke) on the observed scale corrected for principal components. AUC=area under receiver operating characteristic curve. OR=odds ratio. CI=confidence interval

**Table 3**

Sign tests of directional effects among 94 genome-wide significant associations with schizophrenia ( $P < 5 \times 10^{-8}$ ) and the top 231 associations ( $P < 1 \times 10^{-6}$ ).

Brain region	<i>P</i> threshold	N same direction	Proportion	<i>P</i>
Intracranial volume	$< 5 \times 10^{-8}$	49	0.52	0.379
Caudate nucleus	$< 5 \times 10^{-8}$	47	0.50	0.541
Hippocampus	$< 5 \times 10^{-8}$	46	0.49	0.621
Nucleus accumbens	$< 5 \times 10^{-8}$	48	0.51	0.459
Pallidum	$< 5 \times 10^{-8}$	51	0.54	0.235
Putamen	$< 5 \times 10^{-8}$	52	0.55	0.177
Thalamus	$< 5 \times 10^{-8}$	49	0.52	0.379
Amygdala	$< 5 \times 10^{-8}$	49	0.52	0.379
Intracranial volume	$< 1 \times 10^{-6}$	121	0.52	0.255
Caudate nucleus	$< 1 \times 10^{-6}$	113	0.49	0.653
Hippocampus	$< 1 \times 10^{-6}$	105	0.45	0.926
Nucleus accumbens	$< 1 \times 10^{-6}$	109	0.47	0.821
Pallidum	$< 1 \times 10^{-6}$	117	0.51	0.448
Putamen	$< 1 \times 10^{-6}$	115	0.50	0.552
Thalamus	$< 1 \times 10^{-6}$	115	0.50	0.552
Amygdala	$< 1 \times 10^{-6}$	109	0.47	0.821

The expected proportion under the null is 0.5.